Cannabis Studies and Reviews

Latin Name: Cannabis sativa, C. Indica

COMPONENTS: Over 400 constituents have been identified in Cannabis, including Vitamin A, Steroids, flavonoids, terpenoids, and more than 60 Cannabinoids.

CANNABINOIDS are a family of complex molecules that exert most of their actions by binding to and activating specific receptors in the body named cannabinoid receptors, which include CB1 (Central receptor) and CB2 (Peripheral receptor) respectively. The transient receptor potential vanilloid type 1 (TRPV1) has been described as an additional receptor target for several cannabinoids, but the majority of the effects of cannabinoids are mediated via CB1 and CB2.

The cannabinoid receptors (CB1, CB2,TRPV1) are widely distributed throughout the body and regulate a variety of central and peripheral functions, including neuronal development, neuromodulatory processes, energy metabolism, as well as cardiovascular, respiratory, and reproductive functions.

The central nervous system and most of the peripheral effects of cannabinoids rely on CB1 receptor activation. CB1 receptors are located throughout the body, with their highest presence found in the central nervous system (basal ganglia, hippocampus, cerebellum and cortex) where they mediate cannabinoid psychoactive effects. CB1 receptors are also present in peripheral nerve terminals, as well as in non-neural tissues such as testis, uterus, vascular endothelium, eye, spleen, ileum and in adipocytes (fat cells). CB2 receptor expression is mostly restricted to particular elements of the immune system (enriched area of B lymphocyte).

Cannabinoid receptors and their endogenous ligands (binding molecules) have been used as recognized molecular targets for the treatment of various diseases, including neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Huntington's disease, etc.), neuropathic and inflammatory pain, glaucoma, multiple sclerosis, cardiovascular disorders and obesity, etc.

CANNABINOIDS are divided into 3 main categories according to their source of production. 1- Phytocannabinoids (from plants); 2- Endocannabinoids (found inside the body); and 3- Synthetic Cannabinoids

The best known cannabinoids are listed here along with each cannabinoid’s identified target receptor (CB1, CB2, or TRPV1) and the recognized effects of the receptor’s activation or modulation. For a more thorough list of cannabinoids, see the Appendix.

1- PHYTOCANNABINOIDS (Plant-derived). The cannabis plant is the only known natural source of phytocannabinoids of any significant quantity. They are concentrated in a viscous resin that is produced in glandular structures of the plant, known as trichomes. The best known phytocannabinoids are:

   - Δ9- tetrahydrocannabinol (THC), also known as Delta-9 THC, or even just THC - binds with similar affinities for both CB1 and CB2 receptors. It behaves as a CB1 receptor partial agonist (activator). THC is the primary psychoactive cannabis

ingredient, causing: Relaxation; Euphoria; Alteration of Visual, Auditory and Olfactory senses; Disorientation. Possible side-effects with overdose: Anxiety; Panic; temporary Toxic Psychosis.
-Analgesic, antiemetic, appetite stimulant tumor growth inhibitor. Other medicinal effects include: Appetite stimulation; Analgesic (pain relief); Anti-Spasmodic; Anti-Tremor; Anti-Inflammatory; Anti-Nausea

- Δ8-tetrahydrocannabinol (Δ8-THC) or Delta-8 THC; CB1/CB2 agonist. Has similar affinities both for CB1 and CB2 receptors. Is less psychoactive than Delta-9 THC.
  -Anti-tumor agent, inhibitors of mitochondrial O2 consumption in human sperm, antiemetic, appetite stimulant

- Cannabidiol (CBD); CB1 agonist
  -Anti-tumor agent, attenuate catalepsy (muscular rigidity and decreased sensitivity to pain), immunosuppressive, inflammatory or anti-inflammatory agent (depends upon used concentration of drug), antipsychotics (moderates THC). Other medicinal effects include: Anti-convulsant; antioxidant; neuroprotective; immune-modulatory

- Cannabinol (CBN) is a weakly psychoactive cannabinoid, found only in trace amounts in Cannabis

- Cannabigerol (CBG)
  -Multiple sclerosis, antiemetic, anti-inflammatory agent, treatment for neurological disorder

- Cannabichromene (CBC)
  -anti-inflammatory agent, treatment for neurological disorder, hypomotility, antinociception, catalepsy, and hypothermia

- Tetrahydrocannabivarin (THCV)
  -Hepatic ischaemia, anti-inflammatory

- Cannabigerovarin (CBGV)
  -Anti-inflammatory

2- ENDOCANNABINOIDS (Found inside the body). Endogenous cannabinoids are produced in our body and include lipid molecules containing long-chain polyunsaturated fatty acids, amides, esters and ethers that bind to CB1 or CB2 receptors. Several pharmacological evidences show that endocannabinoids also exert biological effects through non-CB1/CB2 receptors.

Endocannabinoids mainly act as neuromodulators or retrograde messengers which affect the release of various neurotransmitters in the peripheral and neural tissues. They also play an important role in inflammation, insulin sensitivity, and fat and energy metabolism. Inhibition of endocannabinoids may be a tool in reducing the prevalence of metabolic syndrome (conditions associated with metabolism, such as obesity, glucose intolerance, insulin resistance, raised blood pressure, etc.).

- N-arachidonoylethanolamine (AEA-anandamide); CB1 agonist (activator) - was isolated from porcine brain in 1992. It was shown as the first brain metabolite to function as a ligand for CB1. It affects our mood, appetite, pain sensation, inflammation response, and memory.
  -Analgesic, antiemetic, appetite stimulant, tumor growth inhibitor

- 2-arachidonoylglycerol (2-AG); CB1/CB2 agonist - was isolated from canine gut. It acts through both CB1 and CB2 receptors. It also affects our mood, appetite, pain sensation, inflammation response, and memory.
  -Analgesic, antiemetic, appetite stimulant, tumor growth inhibitor

- Palmitoyl-ethanolamide (PEA), or N-(2-Hydroxyethyl) hexadecamide (N-acyl-ethanolamide); CB2 agonist. Is co-synthesized with anandamide in all tissues and acts through CB2.
  -Neuromodulatory and immunomodulatory

- Oleamide, or cis-9-octadecenoamide; CB1 agonist - has also been isolated and shown to have similar actions to anandamide in behavioral rodent tests.
  -Neuromodulatory and immunomodulatory

3- SYNTHETIC CANNABINOIDS. Synthetic cannabinoids are created in the lab to provide a consistent, renewable source of cannabinoids that can be used to obtain more detailed insight of cannabinoid action, in order to evaluate their potential clinical use. They showed both anti-tumor and pro-tumor activity, depending on the type of agonist (activator), target tissues, route of administration, doses and duration of the treatment. Synthetic cannabinoids are classified on the basis of chemical structure of molecules and they are capable of a more selective activation of cannabinoid receptor.

- HU-210; CB1/ CB2 Nonselective agonist (activator)
  -Analgesic, multiple sclerosis, neuroprotective

- CP-55,940; CB1/ CB2 Nonselective agonist
  -Anti-cancer agent, Analgesic, antiemetic, appetite stimulant.

- R-(+)-WIN 55,212-2; CB1/ CB2 Nonselective agonist
  -Analgesic, Antiemetic, appetite stimulant, tumor growth inhibitor, multiple sclerosis

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OVERVIEW of Therapeutic Uses of Cannabis and Cannabinoids

RESEARCH REVIEW: Cannabis sativa and Health. Recent advances in medicinal use of Cannabis sativa.

Preparations from Cannabis sativa (marijuana) have been used for many centuries both medicinally and recreationally.

Recent advances in the knowledge of its pharmacological and chemical properties in the organism, mainly due to Delta(9)-tetrahydrocannabinol, and the physiological roles played by the endocannabinoids have opened up new strategies in the treatment of neurological and psychiatric diseases.

Potential therapeutic uses of cannabinoid receptor agonists include the management of spasticity and tremor in multiple sclerosis/spinal cord injury, pain, inflammatory disorders, glaucoma, bronchial asthma, cancer, and vasodilation that accompanies advanced cirrhosis. CB1 receptor antagonists (blockers) have therapeutic potential in Parkinson's disease. (Alsasua 2006)

Alsasua del Valle A. Implication of cannabinoids in neurological diseases. Cell Mol Neurobiol. 2006 Jul-Aug;26(4-6):579-91. Epub 2006 May 12. [PubMed]

STUDY of STUDIES: Cannabinoids in Health. Anorexia, emesis, pain, inflammation, multiple sclerosis, neurodegenerative disorders, epilepsy, glaucoma, osteoporosis, schizophrenia, cardiovascular disorders, cancer, obesity, & metabolic syndrome, are treated by cannabinoid agonists / antagonists/ cannabinoid-related compounds. (Kogan 2007)

Kogan, Natalya M., MSc and Raphael Mechoulam, PhD. Cannabinoids in health and disease.Dialogues Clin Neurosci. Dec 2007; 9(4): 413–430. [PubMed] [Free PMC Article]

STUDY of CANCER STUDIES: Cannabinoids and Cancer. (Chakravarti 2014)

Chakravarti B, Ravi J, Ganju RK. Cannabinoids as therapeutic agents in cancer: current status and future implications. Onco. 2014 Aug 15;5(15):5852-72. [PubMed] [PMC Free Article]

ANTI-EMETIC (Anti-Vomiting) and IMPROVED APPETITE in HIV AIDS, Cancer Chemotherapy and Anorexia Nervosa

REVIEW: Anti-emetic. The anti-emetic efficacy of cannabinoids in cancer patients receiving chemotherapy was evaluated using a systematic review of literature & the

superiority of the anti-emetic efficacy of cannabinoids was demonstrated through meta-analysis. (Rocha 2008)

Machado Rocha FC, Stéfano SC, De Cássia Haiek R, Rosa Oliveira LM, Da Silveira DX. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. Eur J Cancer Care (Engl). 2008 Sep;17(5):431-43. doi: 10.1111/j.1365-2354.2008.00917.x. Epub 2008 Jul 9. [PubMed]

REVIEW: Nausea with Chemo or AIDS; Pain. The effectiveness of the cannabinoids in the treatment of nausea and vomiting due to anti-neoplastic chemotherapy and in the wasting-syndrome during AIDS is recognized. The cannabinoids are also analgesic, and their activity is comparable to the weak opioids. (Shaladi 2008)

Shaladi AM, Crestani F, Tartari S, Piva B. Cannabinoids in the control of pain. Recenti Prog Med. 2008 Dec;99(12):616-24. [Article in Italian] [PubMed]

SURVEY: PG Nausea and Vomiting. Cannabis sativa may be used therapeutically to mitigate pregnancy-induced nausea and vomiting and the paper presents the results of a survey of 84 female users of medicinal cannabis, recruited through two compassion societies in British Columbia, Canada. (Westfall 2006)

Westfall RE, Janssen PA, Lucas P, Capler R. Survey of medicinal cannabis use among childbearing women: patterns of its use in pregnancy and retroactive self-assessment of its efficacy against 'morning sickness'. Complement Ther Clin Pract. 2006 Feb;12(1):27-33. Epub 2005 Dec 22. [PubMed]

STUDIES in culture and animal models: Inhibit tumor cells and exert anti-nausea, anti-vomiting and anti-pain effects. Cannabinoids, the active components of Cannabis sativa and their derivatives, exert palliative effects in cancer patients by preventing nausea, vomiting and pain and by stimulating the appetite. These compounds have been shown to inhibit the growth of tumor cells in culture and animal models. (Guzmán 2003)

Guzmán M. Cannabinoids: potential anticancer agents. Nat Rev Cancer. 2003 Oct;3(10):745-55. [PubMed]

STUDY REVIEW: 80% antiemetic efficacy. The major active constituent of cannabis sativa, delta-9-tetrahydrocannabinol and synthetic cannabinoids are evaluated in several clinical trials on their antiemetic efficacy in cancer chemotherapy induced vomiting. (Heim 1982)

Heim ME. Cannabis and cannabinoids. Possibilities of their therapeutic use. Fortschr Med. 1982 Mar 4;100(9):343-6. [Article in German] [PubMed]

REVIEW: Nausea, Wasting-away conditions. The clinically proven effects in the treatment of pain, cachexia [wasting away] in conjunction with HIV, or malignant disease and treatment of nausea and vomiting, in conjunction with chemotherapy results in prescription of cannabinoids as valuable medication. (Storr 2006)

Storr M, Yüce B, Göke B. Perspectives of cannabinoids in gastroenterology. Z Gastroenterol. 2006 Feb;44(2):185-91. [Article in German] [PubMed]

REVIEW: Appetite-stimulating. The appetite-stimulating effects of the Cannabis sativa have been known since ancient times. The exciting progress in the understanding of how the endocannabinoid CB receptor systems influence appetite and body weight is stimulating the development of therapeutic orexigenic (appetite stimulation) and anorectic (appetite limiting) agents. (Fride 2005)

Fride E, Bregman T, Kirkham TC. Endocannabinoids and food intake: newborn suckling and appetite regulation in adulthood. Exp Biol Med (Maywood). 2005 Apr;230(4):225-34. [PubMed]

12 Month STUDY: Appetite Improvement. Effects of long-term (12 month) use of dronabinol (synthetic THC, known as Marinol and approved for the treatment of nausea and vomiting in cancer and AIDS patients) in 94 late-stage AIDS patients showed consistent improvement in appetite, and found to be safe and effective for anorexia associated with weight loss in patients with AIDS. (Beal 1997)

Beal JE., Olson R., Lefkowitz L., et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. J Pain Symptom Manage. 1997;14:7–14. [PubMed]

STUDY TRIALS: Appetite stimulating. In clinical trials with 139 patients with AIDS-related anorexia, weight was stable in dronabinol (synthetic THC) patients, while placebo recipients lost weight. Improvement in mood and decreased nausea were also noted with dronabinol use. (Beal 1995) (Gorter 1992)

Beal JE., Olson R., Laubenstein L., et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage. 1995;10:89–97. [PubMed]

Gorter R., Seefried M., Volberding P. Dronabinol effects on weight in patients with HIV infection. AIDS. 1992;6:127. [PubMed]

STUDY: HIV appetite. Dronabinol (Synthetic THC) was found to be safe and effective for treatment of HIV wasting syndrome. (Timpone 1997)

Timpone JG., Wright DJ., Li N., et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment

of HIV wasting syndrome. The DATRI 004 Study Group. Division of AIDS Treatment Research Initiative. AIDS Res Hum Retroviruses. 1997;13:305–315. [PubMed]

STUDY REVIEW: Appetite stimulation. Dronabinol (Synthetic THC) showed higher efficacy in stimulating appetite in patients with AIDS as well as in patients with Morbus Alzehimer when compared with placebo. In cancer patients, cannabinoids proved more effective than placebo. (Nauck 2004)

Nauck F., Klaschik E. Cannabinoids in the treatment of the cachexiaanorexia syndrome in palliative care patients. Schmerz. 2004;18:197–202. [PubMed]

STUDY: Appetite Stimulant. Dronabinol (Synthetic THC) was found to be an effective appetite stimulant in patients with advanced cancer, and well tolerated at low doses. (Nelson 1994)

Nelson K., Walsh D., Deeter P., Sheehan F. A phase II study of delta-9-tetrahydrocannabinol for appetite stimulation in cancer-associated anorexia. J Palliat Care. 1994;10:14–18. [PubMed]

REVIEW: Appetite Stimulant; Anti-Nausea. Possible appetite stimulation and antiemetic mechanisms of actions. (Martin 2004)

Martin BR., Wiley JL. Mechanism of action of cannabinoids: how it may lead to treatment of cachexia, emesis, and pain. J Support Oncol. 2004;2:305–314; discussion 314-306. [PubMed]

STUDY: Nausea and cancer in children. Study of eight children, aged 3-13 years with Delta-8-THC (has lower psychotropic activity). It was started two hours before each antineoplastic treatment and continued every 6 hours for 24 hours. Vomiting was completely prevented. Side effects observed were negligible. (Abrahamov 1995)

Abrahamov A., Abrahamov A., Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. Life Sci. 1995;56:2097–2102. [PubMed]

STUDY REVIEW: Anti-emetic. Cannabinoids are more effective antiemetics than the dopamine receptor antagonists such as chlorpromazinetype drugs. (Tramer 2001)

Tramer MR., Carroll D., Campbell FA., Reynolds DJ., Moore RA., McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ. 2001;323:16–21. [PMC Free Article] [PubMed]

PAIN

STUDY REVIEW: Sleep; Pain. This review examines modern studies on effects of Delta9-tetrahydro cannabinol & cannabidiol on sleep in patients with a wide variety of pain conditions including multiple sclerosis, peripheral neuropathic pain, intractable cancer pain & rheumatoid arthritis, with an acceptable adverse event profile. (Russo 2007)

Russo EB. History of cannabis and its preparations in saga, science, and sobriquet. Chem Biodivers. 2007 Aug;4(8):1614-48. [PubMed]

STUDY: Pain and Sleep. Randomized controlled trial with 48 patients: Whole plant use for pain reduction and better sleep. Mild improvement was noted with cannabis-based medicines for treatment of chronic pain associated with brachial plexus (nerve complex in the neck) root avulsion (separation). All 48 patients had intractable symptoms regardless of their current pain therapy. Conclusion: “pain severity score during the last 7 days of treatment failed to fall by the two points defined in our hypothesis. However, both this measure and measures of sleep showed statistically significant improvements.” (Berman 2004)

Berman JS., Symonds C., Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomized controlled trial. Pain. 2004;112:299–306. [PubMed]

STUDY: MS; Pain. 24 MS patients aged 23 - 55 years with central pain participated in a randomized double-blind placebo controlled crossover trial. Median spontaneous pain intensity was significantly lower on THC treatment than on placebo treatment, and median pain-relief score was higher. (Svendsen 2004)

Svendsen KB., Jensen TS., Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ. 2004;329:253. [PMC Free Article] [PubMed]

STUDY: MS; Pain. 24 MS patients participated in a double-blind placebo-controlled crossover trial with dronabinol (synthetic THC) reduced the spontaneous pain intensity significantly compared with placebo, showing it can be effective in treating central pain [Central Nervous System pain]. (Svendsen 2005)

Svendsen KB., Jensen TS., Bach FW. Effect of the synthetic cannabinoid dronabinol on central pain in patients with multiple sclerosis - secondary publication. Ugeskr Laeger. 2005;167:2772–2774. [PubMed]

TRIAL: Cancer and Pain. Single oral doses of THC to patients with cancer pain demonstrated a mild analgesic effect. Pain relief significantly superior to placebo was

demonstrated at high dose levels. Substantial sedation and mental clouding were reported at higher levels. (Noyes 1975) (Noyes 1975)

Noyes R., Jr., Brunk SF., Avery DA., Canter AC. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clin Pharmacol Ther. 1975;18:84–89. [PubMed]

Noyes R., Jr., Brunk SF., Baram DA., Canter A. Analgesic effect of delta-9-tetrahydrocannabinol. J Clin Pharmacol. 1975;15:139–143. [PubMed]

SURVEY: Non-cancer pain. Patients who suffer from pain tend to self-medicate with marijuana. In an anonymous cross-sectional survey, 72 (35 %) of chronic non-cancer pain patients reported having used cannabis for relieving pain. (Ware 2003)

Ware MA., Doyle CR., Woods R., Lynch ME., Clark AJ. Cannabis use for chronic non-cancer pain: results of a prospective survey. Pain. 2003;102:211–216. [PubMed]

STUDY: HIV Nausea, pain and other symptoms. Anonymous cross-sectional questionnaire: HIV-positive individuals attending a large clinic were recruited for this study. Up to one-third (27%, 143/523) reported using cannabis for treating symptoms. Patients reported improved appetite (97%), muscle pain (94%), nausea (93%), anxiety (93%), nerve pain (90%), depression (86%), and paresthesia (85%). Many cannabis users (47%) reported associated memory deterioration. (Woolridge 2005)

Woolridge E., Barton S., Samuel J., Osorio J., Dougherty A., Holdcroft A. Cannabis use in HIV for pain and other medical symptoms. J Pain Symptom Manage. 2005;29:358–367. [PubMed]

CLINICAL Observational STUDY: Nausea and vomiting. Clinical experience of 20 adult patients with chronic noncancer pain who had been treated with nabilone (a synthetic cannabinoid) with lower psychotropic side effects, and followed up for an average of 1.5 years. Prior to nabilone therapy, patients had used a wide range of therapies, including 11 who had used cannabis. Fifteen patients reported subjective overall improvement with nabilone, and nine reported reduced pain intensity. Beneficial effects on sleep and nausea were the main reasons for continuing use. (Berlach 2006)

Berlach DM., Shir Y., Ware MA. Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. Pain Med. 2006;7:25–29. [PubMed]

STUDY: Spasticity-related pain. In a double-blind placebo-controlled cross-over trial with a low-dose synthetic cannabinoid Nabilone (has lower psychotropic side effects) Test, a significant decrease in disabling spasticity-related pain of patients with chronic upper motor neuron syndrome (UMNS) was found. It was noted that spasticity, motor function and activities of daily living did not appear to change. (Wissel 2006)

Wissel J., Haydn T., MuIler J., et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. J Neurol. 2006;253:1337–1341. [PubMed]

STUDY: Reduction of chronic neuropathic pain in a randomized controlled trial. Ajulemic acid (AJA), a cannabinoid, was effective in reducing chronic neuropathic pain, although cannabinoid side effects (tiredness, dry mouth, limited power of concentration, dizziness, sweating) were noted. (Karst 2003)

Karst M., Salim K., Burstein S., Conrad I., Hoy L., Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. JAMA. 2003;290:1757–1762. [PubMed]

META-STUDY ANALYSIS: MS Pain with Sativex. The CBD/THC buccal spray (Sativex) was found to be effective in treating neuropathic pain in multiple sclerosis (MS). (Iskedjian 2007)

Iskedjian M., Bereza B., Gordon A., Piwko C., Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. Curr Med Res Opin. 2007;23:17–24. [PubMed]

STUDY REVIEW: MS Pain; Better sleep. Chronic neuropathic pain can be treated with cannabis extracts containing THC, or CBD, or with Sativex. The latter also was effective in reducing sleep disturbances in these patients and was mostly well tolerated. (Notcutt 2004) (Rog 2005)

Notcutt W., Price M., Miller R., et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. Anaesthesia. 2004;59:440–452. [PubMed]

Rog DJ., Nurmikko TJ., Friede T., Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005;65:812–819. [PubMed]

STUDIES: MS spasticity and Pain. In placebo-controlled trials of the use of Sativex demonstrate that Sativex is efficacious and well tolerated in the treatment of spasticity and neuropathic pain. Sativex is the first cannabis-based medicine to undergo conventional clinical development and to be approved as a prescription drug in Canada. (Barnes 2006)

Barnes MP. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. Exp Opin Pharmacother. 2006;7:607–615. [PubMed]

SLEEP

SLEEP STUDY REVIEW: Sleep. THC is sedative, while CBD has alerting properties as it increased awake activity and counteracted the residual sedative activity of THC. (Nicholson 2004)

Nicholson AN., Turner C., Stone BM., Robson PJ. Effect of Delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. J Clin Psychopharmacol. 2004;24:305–313. [PubMed]

OBSERVATIONAL STUDIES: Effects of THC on Sleep. Administration of THC significantly reduced eye movement activity during sleep with rapid eye movements (REM) and, to a lesser extent, the duration of REM itself. The effects on sleep of THC administration closely resemble those induced by lithium. (Feinberg 1976) (Feinberg 1975)

Feinberg I., Jones R., Walker J., Cavness C., Floyd T. Effects of marijuana extract and tetrahydrocannabinol on electroencephalographic sleep patterns. Clin Pharmacol Ther. 1976;19:782–794. [PubMed]

Feinberg I., Jones R., Walker JM., Cavness C., March J. Effects of high dosage delta-9-tetrahydrocannabinol on sleep patterns in man. Clin Pharmacol Ther. 1975;17:458–466. [PubMed]

MULTIPLE SCLEROSIS (MS); SPASTICITY; NEUROPROTECTION; INFLAMMATION

Cannabis and its derivatives relieve pain related to MS [See PAIN section above for studies]. Spasticity is a common neurologic condition in patients with MS, stroke, cerebral palsy, or an injured spinal cord. Inflammation, autoimmune response, demyelination, and axonal damage are thought to participate in the pathogenesis of MS. Increasing evidence supports the idea of a beneficial effect of cannabinoid compounds for the treatment of this disease.

RESEARCH ARTICLE: Spasticity. Marijuana was suggested as treatment of muscle spasticity as early as the 1980s. (Petro 1980)

Petro DJ. Marihuana as a therapeutic agent for muscle spasm or spasticity. Psychosomatics. 1980;21:81–85. [PubMed]

RESEARCH ARTICLE: Inflammation; Arthritis; MS. Cannabinoids have been shown to modulate a variety of immune cell functions & have therapeutic implications on central nervous system inflammation, chronic inflammatory conditions such as arthritis & may

be therapeutically useful in treating autoimmune conditions like multiple sclerosis. (Woelkart 2008)

Woelkart K, Salo-Ahen OM, Bauer R. CB receptor ligands from plants. Curr Top Med Chem. 2008;8(3):173-86. [PubMed]

STUDY: MS with Lower Urinary Tract Symptoms LUTS. 15-patients with advanced MS and refractory LUTS were evaluated in an open trial. Results showed urinary urgency, number and volume of incontinence episodes, frequency and nocturia all decreased significantly following treatment with THC/ CBD Cannabis combination extract. A patient self-assessment of pain, spasticity and quality of sleep showed significant improvement. Few troublesome side effects were noted, suggesting it was a safe and effective treatment. (Brady 2004)

Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. Mult Scler. 2004 Aug;10(4):425-33. [PubMed]

STUDY: Spasms with MS. 57 patients were enrolled in a prospective, randomized, double-blind, placebo-controlled crossover study of cannabis-extract capsules. Trends in favor of active treatment were seen for spasm frequency, mobility and getting to sleep. CONCLUSION: A standardized Cannabis sativa plant extract might lower spasm frequency and increase mobility with tolerable side effects in MS patients with persistent spasticity not responding to other drugs. (Vaney 2004)

Vaney C, Heinzel-Gutenbrunner M, Jobin P, Tschopp F, Gattlen B, Hagen U, Schnelle M, Reif M. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. Mult Scler. 2004 Aug;10(4):417-24. [PubMed]

Observational STUDY: Spasms. A patient with generalized dystonia [abnormal muscle tone, may cause jerking] due to Wilson's disease obtained marked improvement in response to smoking cannabis. (Roca 2004)

Uribe Roca MC, Micheli F, Viotti R. Cannabis sativa and dystonia secondary to Wilson's disease. Mov Disord. 2005 Jan;20(1):113-5. [PubMed]

REVIEW: Neuroprotective and Growth-inhibiting. The neuroprotective effect of cannabinoids has potential clinical relevance for treatment of neurodegenerative disorders such as multiple sclerosis, Parkinson's disease, & ischemia/stroke, whereas their growth-inhibiting action on transformed cells is useful for malignant brain tumors. (Guzmán 2001)

Guzmán M, Sánchez C, Galve-Roperh I. Control of the cell survival/death decision by cannabinoids. J Mol Med (Berl). 2001;78(11):613-25. [PubMed]

IN VIVO (rats) STUDY: With implications for CNS Inflammation with MS. In experimental rat autoimmune encephalomyelitis (EAE), a laboratory model of MS, THC, given once after disease onset, significantly reduced maximal EAE score. Reduction in the inflammatory response in the brain and spinal cord was also noted in animals treated with dexanabinol (HU-211 a nonpsychoactive synthetic cannabinoid). (Achiron 2000)

Achiron A., Miron S., Lavie V., Margalit R., Biegon A. Dexanabinol (HU-211) effect on experimental autoimmune encephalomyelitis: implications for the treatment of acute relapses of multiple sclerosis. J Neuroimmunol. 2000;102:26–31. [PubMed]

IN VIVO (rats)TRIAL: With implications for CNS. Inflammation with MS Rats treated with placebo developed severe clinical EAE and more than 98% died, while THC-treated animals had either no clinical signs or mild signs, with delayed onset with survival greater than 95%. (Lyman 1989)

Lyman WD., Sonett JR., Brosnan CF., Elkin R., Bornstein MB. Delta 9-tetrahydrocannabinol: a novel treatment for experimental autoimmune encephalomyelitis. J Neuroimmunol. 1989;23:73–81. [PubMed]

IN VIVO STUDY RESEARCH: With MS Implications. WIN-55,212-2 (synthetic cannabinoid), was found to ameliorate the clinical signs of EAE and to diminish cell infiltration of the spinal cord, partially through CB2. Results may open new therapeutic doors in the management of MS by non-psychoactive selective cannabinoid agonists. (Sanchez 2006)

Sanchez AJ., Gonzalez-Perez P., Galve-Roperh I., Garcia-Merino A. R-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphta!enylmethanone (WIN-2) ameliorates experimental autoimmune encephalomyelitis and induces encephalitogenic T cell apoptosis: partial involvement of the CB(2) receptor. Biochem Pharmacol. 2006;72:1697–1706. [PubMed]

IN VIVO (mice) STUDY: Neuroprotection with MS implications. Using a chronic model of MS in mice, it was shown that clinical signs and axonal damage in the spinal cord were reduced by the synthetic cannabinoid HU210. (Docagne 2007)

Docagne F., Muneton V., Clemente D., et al. Excitotoxicity in a chronic model of multiple sclerosis: Neuroprotective effects of cannabinoids through CB1 and CB2 receptor activation. Mol Cell Neurosci. 2007;34:551–561. [PubMed]

IN VIVO (mice) TRIAL: With implications for MS treatment. In mice with chronic relapsing experimental allergic encephalomyelitis (CREAE), a chronic model of MS that reproduces many of the pathological hallmarks of the human disease, a moderate decrease in the density of CB1 receptors in the caudate-putamen, globus pallidus, and cerebellum was found. These observations may explain the efficacy of cannabinoid agonists in improving motor symptoms (spasticity, tremor, ataxia) typical of MS in both humans and animal models. (Cabranes 2006)

Cabranes A., Pryce G., Baker D., Fernandez-Ruiz J. Changes in CB1 receptors in motor-related brain structures of chronic relapsing experimental allergic encephalomyelitis mice. Brain Res. 2006;1107:199–205. [PubMed]

IN VIVO (mice) TRIAL: With implications for MS treatment. In an experiment with mice, control of spasticity in a MS model was found to be mediated by CB1, but not by CB2, cannabinoid receptors. (Pryce 2007)

Pryce G., Baker D. Control of spasticity in a multiple sclerosis model is mediated by CB1, not CB2, cannabinoid receptors. Br J Pharmacol. 2007;150:519–525. [PMC Free Article] [PubMed]

CLINICAL STUDIES: MS Spasticity. In clinical trials, patients treated with THC had significant improvement in ratings of spasticity compared to placebo. (Ungerleider 1987)

Ungerleider JT., Andyrsiak T., Fairbanks L., Ellison GW., Myers LW. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. Adv Alcohol Subst Abuse. 1987;7:39–50. [PubMed]

CASE REPORT: Spasms; Nocturia. In one case report nabilone improved muscle spasms, nocturia, and general well-being. (Martyn 1995)

Martyn CN., Illis LS., Thom J. Nabilone in the treatment of multiple sclerosis. Lancet. 1995;345:579. [PubMed]

CASE REPORT: MS spasticity. Chronic motor handicaps of an MS patient were acutely improved while he smoked a marijuana cigarette. (Meinck 1989)

Meinck HM., Schonle PW., Conrad B. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. J Neurol. 1989;236:120–122. [PubMed]

STUDY: MS Spasticity. Muscle tone, reflexes, strength and performed EMGs before and after double-blinded oral administration of THC or placebo were tested. THC significantly reduced spasticity. Quadriceps EMG interference pattern was reduced. Benefit was seen with ‘tonic spasm’ patients. No benefit was noted in patients with cerebellar disease. (Petro 1981)

Petro DJ., Ellenberger C., Jr. Treatment of human spasticity with delta-9-tetrahydrocannabinol. J Clin Pharmacol. 1981;21:413S–416S. [PubMed]
2-PATIENT STUDY: Spasticity. At a progressive stage of illness, oral and rectal THC reduced the spasticity, rigidity, and pain, resulting in improved active and passive mobility. (Brenneisen 1996)

Brenneisen R., Egli A., Elsohly MA., Henn V., Spiess Y. The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. Int J Clin Pharmacol Ther. 1996;34:446–452. [PubMed]

CLINICAL TRIALS: MS tremor reduction. Cannabinoids appeared to reduce tremor but were ineffective in spasticity. Inconsistent effects might be due to insufficient dose. (Koch 2007) (Killestein 2002) (Clifford 1983)

Koch M., Mostert J., Heersema D., De Keyser J. Tremor in multiple sclerosis. J Neurol. 2007;254:133–145. [PMC Free Article] [PubMed]

Killestein J., Hoogervorst EL., Reif M., et al. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. Neurology. 2002;58:1404–1407. [PubMed]
OBSERVATIONAL REPORT: Tremor with MS. Improved motor coordination was seen when patients with MS, seriously disabled with tremor and ataxia (lack of coordination), were given oral THC. (Clifford 1983)

Clifford DB. Tetrahydrocannabinol for tremor in multiple sclerosis. Ann Neurol. 1983;13:669–671. [PubMed]

OBSERVATIONAL REPORT: MS with Eye Movement. Suppression of acquired pendular nystagmus (involuntary movement of the eyes) was seen in a patient with MS after smoking cannabis resin, but not after taking nabilone tablets or orally administered capsules containing cannabis oil. (Schon 1999)

Schon F., Hart PE., Hodgson TL., et al. Suppression of pendular nystagmus by smoking cannabis in a patient with multiple sclerosis. Neurology. 1999;53:2209–2210. [PubMed]

LARGE STUDY: MS with incontinence. Multicentre randomized trial of the Cannabinoids in randomized with 630 MS patients. They received oral administration of either cannabis extract, Delta-9 THC, or placebo. Subjects completed incontinence diaries. Study groups showed a significant reduction in episode rate over placebo: cannabis extract, 38%; THC, 33%; and placebo, 18%. Findings suggest a clinical effect of cannabis on incontinence episodes in patients with MS. (Freeman 2006)

Freeman RM., Adekanmi O., Waterfield MR., Waterfield AE., Wright D., Zajicek J. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMSLUTS). Int Urogynecol J Pelvic Floor Dysfunct. 2006;17:636–641. [PubMed]

REVIEW: MS Treatment. Company filing for approval for the treatment of MS with Sativex in the UK and Canada. In the treatment of MS and pain reduction there is a preferential effect of a THC+CBD combination (Sativex). (Smith 2004)

Smith PF. GW-1000. GW Pharmaceuticals. Curr Opin Investig Drugs. 2004;5:748–754. [PubMed]

STUDY: MS Spasticity not responding to other drugs. A randomized, double-blind, placebo-controlled, crossover study showed a mixture of THC and CBD lowered spasm frequency and increased mobility, with tolerable side effects, in MS patients with persistent spasticity not responding to other drugs. (Vaney 2004)

Vaney C., Heinzel-Gutenbrunner M., Jobin P., et al. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. Mult Scler. 2004;10:417–424. [PubMed]

STUDY: MS and spasticity. Oromucosal sprays of Sativex significantly reduced spasticity scores in comparison with placebo in a double-blind, randomized, placebo-controlled study on 160 patients. (Wade 2004)

Wade DT., Makela P., Robson P., House H., Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Mult Scler. 2004;10:434–441. [PubMed]

STUDY: MS and spasticity. 137 MS patients with symptoms not controlled satisfactorily using standard drugs entered this open-label trial following a 10-week, placebo-controlled study. Unwanted effects were mild to moderate. Results confirmed that long-term use of Sativex maintains its effect in those patients who perceive initial benefit. (Wade 2006)

Wade DT., Makela PM., House H., Bateman C., Robson P. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Mult Scler. 2006;12:639–645. [PubMed]

STUDIES: MS and spasticity. Zajicek et al originally reported that cannabinoids did not have a beneficial effect on spasticity, though there was an objective improvement in mobility and some patients reported an improvement in pain. It was later found that with prolonged treatment, the same group found positive effects on muscle spasticity. (Zajicek 2003) (Zajicek 2005) (Bifulco 2007) (Mestre 2006)

Zajicek J., Fox P., Sanders H., et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet. 2003;362:1517–1526. [PubMed]

Zajicek JP., Sanders HP., Wright DE., et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry. 2005;76:1664–1669. [PMC Free Article] [PubMed]

Bifulco M., Laezza C., Malfitano AM. From anecdotal evidence of cannabinoids in multiple sclerosis to emerging new therapeutical approaches. Mult Scler. 2007;13:133–134. [PubMed]

Mestre L., Correa F., Docagne F., et al. Cannabinoid system and neuroinflammation: therapeutic perspectives in multiple sclerosis. Rev Neurol. 2006;43:541–548. [PubMed]

PARKINSON'S DISEASE (PD)

Parkinson's disease is a chronic, progressive neurodegenerative disorder. A principle feature of Parkinson's is the degeneration of dopamine-containing neurons. The irreversible loss of the dopamine-mediated control of certain brain structures leads to the typical motor symptoms observed in Parkinson's, ie, bradykinesia (abnormal slowness of movement), tremor, and rigidity.

RESEARCH REVIEW: Neurodegenerative diseases. Research regarding manipulation of the endocannabinoid system and its effects on neuroinflammatory and neurodegenerative disorders. The effect of agonists/ antagonists of endocannabinoid receptors, or of inhibitors of endocannabinoid metabolism, is discussed in the context of onset and progression of Huntington's disease, and is compared with other neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, and amyotropic lateral sclerosis (ALS). Also the plastic changes of endocannabinoids in multiple sclerosis will be reviewed, as a paradigm of their impact in neuroinflammatory disorders. It has been proposed that cannabinoids may have some beneficial effects in the treatment. (Maccarrone 2007)

Maccarrone M., Battista N., Centonze D. The endocannabinoid pathway in Huntington's disease: a comparison with other neurodegenerative diseases. Prog Neurobiol. 2007;81:349–379. [PubMed]

STUDY REVIEW of ANIMAL MODELS and CLINICAL TRIALS: Parkinson's Disease. The majority of Parkinson's Disease patients undergoing levodopa therapy develop disabling motor complications (dyskinesias) within 10 years of treatment. Recent studies in animal models and clinical testing suggest that CB1 receptor antagonists could prove useful in the treatment of both parkinsonian symptoms and levodopa-induced dyskinesia [uncontrolled movement], whereas CB1 receptor agonists could have value in reducing levodopa-induced dyskinesia. (Brotchie 2003)

Brotchie JM. CB1 cannabinoid receptor signalling in Parkinson's disease. Curr Opin Pharmacol. 2003;3:54–61. [PubMed]

IN VIVO (rat) EXPERIMENTS: Implications to reducing negative Parkinson's Disease therapy side-effects. Chronic levodopa therapy produced increasingly severe orolingual (oral) involuntary movements which were attenuated (reduced) by WIN 55,212-2. To verify, this process was also reversed by rimonabant (endocanabinoid antagonist). Stimulation of cannabinoid receptors with Delta 9-TCH, is emerging as a promising therapy to alleviate levodopa-associated dyskinesia. These results indicate that a deficiency in endocannabinoid transmission may contribute to levodopa-induced dyskinesias and that these complications may be alleviated by activation of CB1 receptors. (Ferrer 2003)

Ferrer B., Asbrock N., Kathuria S., Piomelli D., Giuffrida A. Effects of levodopa on endocannabinoid levels in rat basal ganglia: implications for the treatment of levodopa-induced dyskinesias. Eur J Neurosci. 2003;18:1607–1614. [PubMed]

IN VIVO (rat) MODEL: With Parkinson's Disease (PD) implications. In the reserpine-treated rat model of PD, the dopamine D2 receptor agonist quinpirole caused a significant alleviation [relief] of the akinesia [loss of motor control]. This effect was significantly reduced by coinjection with the cannabinoid receptor agonist WIN 55,212-2. The simultaneous administration of the CB1 antagonist rimonabant with quinpirole and WIN 55,212-2 blocked the effect of WIN 55,212-2 on quinpirole-induced alleviation of akinesia. (Maneuf 1997)

Maneuf YP., Crossman AR., Brotchie JM. The cannabinoid receptor agonist WIN 55,212-2 reduces D2, but not D1, dopamine receptor-mediated alleviation of akinesia in the reserpine-treated rat model of Parkinson's disease. Exp Neurol. 1997;148:265–270. [PubMed]

IN VITRO and IN VIVO (mice) STUDIES: Neuroprotection with treatment implications for Parkinson's Disease (PD). Daily administration of THC over 2 weeks showed neuroprotective activity. In another study, HU-210, a potent synthetic analog of THC, increases survival of mouse cerebellar granule cells exposed to 6-hydroxydopamine (causes nerve damage). (Lastres-Becker 2005)

Lastres-Becker I., Molina-Holgado F., Ramos JA., Mechoulam R., Fernandez-Ruiz J. Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Parkinson's disease. Neurobiol Dis. 2005;19:96–107. [PubMed]

CLINICAL TRIALS: Intracranial pressure due to head Injury. In randomized, placebo-controlled clinical trials, dexanabinol (synthetic cannabinoid analogue devoid of psychotropic activity)-treated patients achieved significantly better intracranial

pressure/cerebral perfusion pressure control without jeopardizing blood pressure. A trend toward faster and better neurologic outcome was also observed. (Knoller 2002)

Knoller N., Levi L., Shoshan I., et al. Dexanabinol (HU-211) in the treatment of severe closed head injury: a randomized, placebo-controlled, phase II clinical trial. Crit Care Med. 2002;30:548–554. [PubMed]

STUDY with PD patients and marmosets: Parkinson's motor symptoms. Endocanabinoid manipulation with Parkinson's Disease. A nigrostriatal lesion by MPTP is associated with an increase in CB1 receptors in the basal ganglia in humans and nonhuman primates; this increase could be reversed by chronic levodopa therapy, which suggests that CB1 receptor blockade might be useful as an adjuvant for the treatment of parkinsonian motor symptoms. (Lastres-Becker 2001)

Lastres-Becker I., Cebeira M., de Ceballos ML., et al. Increased cannabinoid CB1 receptor binding and activation of GTP-binding proteins in the basal ganglia of patients with Parkinson's syndrome and of MPTP-treated marmosets. Eur J Neurosci. 2001;14:1827–1832. [PubMed]

STUDY: Parkinson's Disease observation. High endogenous cannabinoid levels are found in the cerebrospinal fluid of untreated PD patients. (Pisani 2005)

Pisani A., Fezza F., Galati S., et al. High endogenous cannabinoid levels in the cerebrospinal fluid of untreated Parkinson's disease patients. Ann Neurol. 2005;57:777–779. [PubMed]

IN VIVO STUDY: Parkinson's Disease. Administration of inhibitors of endocannabinoid degradation reduced parkinsonian motor deficits in vivo. (Kreitzer 2007)

Kreitzer AC., Malenka RC. Endocannabinoid-mediated rescue of striatal LTD and motor deficits in Parkinson's disease models. Nature. 2007;445:643–647. [PubMed]

CLINICAL TRIALS: Parkinson's Disease. In clinical trials, the cannabinoid receptor agonist nabilone significantly reduced levodopa-induced dyskinesia in PD. (Sieradzan 2001)

Sieradzan KA., Fox SH., Hill M., Dick JP., Crossman AR., Brotchie JM. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: a pilot study. Neurology. 2001;57:2108–2111. [PubMed]

OBSERVATIONAL STUDY: Motor control. THC improved motor control in a patient with musician's dystonia (loss of motor control). (Jabush 2004)

Jabusch HC., Schneider U., Altenmuller E. Delta9-tetrahydrocannabinol improves motor control in a patient with musician's dystonia. Mov Disord. 2004;19:990–991. [PubMed]

REVIEW: Neurological Diseases. Cannabinoids seem to be able to treat at least some symptoms of neurological diseases. (Alsasua 2006) (Lastres-Becker 2006) (Sevcik 2000)

Alsasua del Valle A. Implication of cannabinoids in neurological diseases. Cell Mol Neurobiol. 2006;26:579–591. [PubMed]

Lastres-Becker I., Fernandez-Ruiz J. An overview of Parkinson's disease and the cannabinoid system and possible benefits of cannabinoid-based treatments. Curr Med Chem. 2006;13:3705–3718. [PubMed]

Sevcik J., Masek K. Potential role of cannabinoids in Parkinson's disease. Drugs Aging. 2000;16:391–395. [PubMed]

HUNTINGTON'S DISEASE (HD)

Huntington's disease (HD) is a disorder characterized by progressive motor movement disturbances, dementia, and other cognitive deficits. Neuropathologically, HD is characterized by a degeneration of (GABA)ergic neurons and by an atrophy of the caudate nucleus. Advanced grades of HD showed an almost total loss of CB1 receptors These findings suggest a possible therapeutic role of cannabinoid agonists in HD. (Glass 2000) (Richfield 1994) (Glass 1993)

Glass M., Dragunow M., Faull RL. The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and GABA(A) receptor alterations in the human basal ganglia in Huntington's disease. Neuroscience. 2000;97:505–519. [PubMed]

Richfield EK., Herkenham M. Selective vulnerability in Huntington's disease: preferential loss of cannabinoid receptors in lateral globus pallidus. Ann Neurol. 1994;36:577–584. [PubMed]

Glass M., Faull RL., Dragunow M. Loss of cannabinoid receptors in the substantia nigra in Huntington's disease. Neuroscience. 1993;56:523–527. [PubMed]

IN VIVO (rat) MODEL STUDY: Huntington's disease (HD). Arvanil, a hybrid endocannabinoid and vanilloid compound, behaves as an antihyperkinetic agent in a rat model of Huntington's disease. Arvanil alleviates hyperkinesia (uncontrolled movement) typical of HD, although it also affects locomotion in normal rats. (deLago 2005)

de Lago E., Urbani P., Ramos JA., Di Marzo V., Fernandez-Ruiz J. Arvanil, a hybrid endocannabinoid and vanilloid compound, behaves as an antihyperkinetic agent in a rat model of Huntington's disease. Brain Res. 2005;1050:210–216. [PubMed]

IN VIVO (rat) MODEL STUDY: Huntington's Disease (HD). Compounds acting at the endocannabinoid and/or endovanilloid systems reduce hyperkinesia in a rat model of

Huntington's disease. Effects of selective direct agonists for VR1 (capsaicin) or CB1 (CP55,940) receptors were tested. Capsaicin exhibited a strong antihyperkinetic activity and, moreover, was able to attenuate the reductions in dopamine and GABA transmission provoked by the 3NP lesion, whereas CP55,940 had also antihyperkinetic activity but was unable to cause recovery of either dopamine or GABA deficits in the basal ganglia. In summary, data indicates a major role for VR1 receptors, as compared to CB1 receptors, in the antihyperkinetic effects and the recovery of neurochemical deficits caused in 3NP-lesioned rats by compounds that activate both CB1 and VR1 receptors, either directly or via manipulation of the levels of endogenous agonists. (Lastres-Becker 2003)

Lastres-Becker I., de Miguel R., De Petrocellis L., Makriyannis A., Di Marzo V., Fernandez-Ruiz J. Compounds acting at the endocannabinoid and/or endovanilloid systems reduce hyperkinesia in a rat model of Huntington's disease. J Neurochem. 2003;84:1097–1109. [PubMed]

IN VIVO (rat) STUDY: Huntington's Disease (HD). The cannabinoid receptor agonist WIN 55,212-2 attenuates (relieves) the negative effects induced by quinolinic acid in the rat striatum (used to reproduce features of HD). (Pintor 2006)

Pintor A., Tebano MT., Martire A., et al. The cannabinoid receptor agonist WIN 55,212-2 attenuates the effects induced by quinolinic acid in the rat striatum. Neuropharmacology. 2006;51:1004–1012. [PubMed]

TOURETTE SYNDROME (TS) is characterized by multiple motor and vocal tics.

24-Patient STUDY: Tourette Syndrome (TS), Delta-9 THC may reduce tics. A randomized, double-blind, placebo-controlled study of 24 patients with Tourette syndrome to investigate under controlled conditions, over a long-term treatment period, found delta-9-tetrahydrocannabinol treatment safe and that it might play a role in reducing tics in TS. No serious adverse effects occurred and no impairment on neuropsychological performance was observed. (Müller-Vahl 2003)

Müller-Vahl KR, Schneider U, Prevedel H, Theloe K, Kolbe H, Daldrup T, Emrich HM. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. J Clin Psychiatry. 2003 Apr;64(4):459-65. [PubMed]

STUDY: Tourette (TS) treatment safe, but not effective. Treatment of Tourette syndrome with delta 9-THC had no influence on neuropsychological performance. In this randomized double-blind placebo-controlled study, we investigated the effect of a

treatment with up to 10 mg Delta(9)-THC over a 6-week period on neuropsychological performance in 24 patients suffering from TS. During medication and immediately as well as 5-6 weeks after withdrawal of Delta(9)-THC treatment, no detrimental effect was seen on learning curve, interference, recall and recognition of word lists, immediate visual memory span, and divided attention. Measuring immediate verbal memory span, we even found a trend towards a significant improvement during and after treatment. Results from this study corroborate previous data suggesting that in patients suffering from TS, treatment with Delta(9)-THC causes neither acute nor long-term cognitive deficits. [PMC Free Article] (Muller-Vahl 2003)

Muller-Vahl KR., Prevedel H., Theloe K., Kolbe H., Emrich HM., Schneider U. Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9-THC): no influence on neuropsychological performance. Neuropsychopharmacology. 2003;28:384–388. [PubMed]

STUDY: Tourette (TS) Tics and Obsessive-compulsive behavior (OCB) improved. In a randomized double-blind placebo-controlled crossover single-dose trial of Delta(9)-THC in 12 adult TS patients. Tic severity was assessed using a self-rating scale and examiner ratings and patients also rated the severity of associated behavioral disorders. There was a significant improvement of tics and obsessive-compulsive behavior (OCB) after treatment with Delta(9)-THC compared to placebo. (Muller-Vahl 2002)

MuIler-VahI KR., Schneider U., Koblenz A., et al. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): a randomized crossover trial. Pharmacopsychiatry. 2002;35:57–61. [PubMed]

STUDY: Tourette (TS) with Single dose of THC. A single-dose treatment (SDT) rules out the possibility of administering the dosage slowly. In contrast to results of healthy marijuana users, a SDT with delta9-THC in patients suffering from TS does not cause cognitive impairment. (Müller-Vahl 2001)

Müller-Vahl KR, Koblenz A, Jöbges M, Kolbe H, Emrich HM, Schneider U. Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. Pharmacopsychiatry. 2001 Jan;34(1):19-24. [PubMed]

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

ALS is a fatal neurodegenerative disorder characterized by a selective loss of motor neurons in the spinal cord, brain stem, and motor cortex.

REVIEW article: ALS. Many effects of cannabis may be applicable to the management of ALS. These include pain reduction, muscle relaxation, broncho-dilation, saliva reduction, appetite stimulation, and sleep induction. In addition, the strong antioxidative and neuroprotective effects of cannabis may prolong neuronal cell survival. (Carter 2001)

Carter GT., Rosen BS. Marijuana in the management of amyotrophic lateral sclerosis. Am J Hosp Palliat Care. 2001;18:264–270. [PubMed]

IN VIVO (mice) TRIAL: Neuroprotection in ALS symptom-induced mice. Treatment with WIN 55,212-2 of post-symptomatic, 90-day-old SOD1G93A mice (a model of ALS), elevated cannabinoid levels and significantly delayed disease progression, but had no effect on life span. Results show that cannabinoids have significant neuroprotective effects in this model of ALS, and suggest that these beneficial effects may be mediated by non-CB1 receptor mechanisms. (Bilsland 2006)

Bilsland LG., Dick JR., Pryce G., et al. Increasing cannabinoid levels by pharmacological and genetic manipulation delay disease progression in SOD1 mice. Faseb J. 2006;20:1003–1005. [PubMed]

IN VIVO (mice) TRIAL: ALS progression delayed. THC was found to delay the progression of ALS. (Raman 2004) (Weydt 2005)

Raman C., McAllister SD., Rizvi G., Patel SG., Moore DH., Abood ME. Amyotrophic lateral sclerosis: delayed disease progression in mice by treatment with a cannabinoid. Amyotroph Lateral Scler Other Motor Neuron Disord. 2004;5:33–39. [PubMed]

Weydt P., Hong S., Witting A., Moller T., Stella N., Kliot M. Cannabinol delays symptom onset in SOD1 (G93A) transgenic mice without affecting survival. Amyotroph Lateral Scler Other Motor Neuron Disord. 2005;6:182–184. [PubMed]

IN VIVO (mice) TRIAL: ALS treatment delayed motor impairment and prolonged survival. Treatment with AM1241, a CB2-selective agonist, was effective at slowing signs of disease progression, when administered after onset of signs in an ALS mouse model. Administration at the onset of tremors delayed motor impairment in treated mice when compared with vehicle controls; moreover, AM-1241 prolonged survival in these mice. (Moore 2006) (Shoemaker 2007)

Kim K., Moore DH., Makriyannis A., Abood ME. AM 1241, a cannabinoid CB2 receptor selective compound, delays disease progression in a mouse model of amyotrophic lateral sclerosis. Eur J Pharmacol. 2006;542:100–105. [PubMed]

Shoemaker JL., Seely KA., Reed RL., Crow JP., Prather PL. The CB2 cannabinoid agonist AM-1241 prolongs survival in a transgenic mouse model of amyotrophic lateral sclerosis when initiated at symptom onset. J Neurochem. 2007;101:87–98. [PMC Free Article] [PubMed]

PATIENT SURVEY: ALS. In a survey among ALS patients, cannabis was reported to be moderately effective in reducing symptoms of appetite loss, depression, pain, spasticity, and drooling. (Amtmann 2004)

Amtmann D., Weydt P., Johnson KL., Jensen MP., Carter GT. Survey of cannabis use in patients with amyotrophic lateral sclerosis. Am J Hosp Palliat Care. 2004;21:95–104. [PubMed]

ALZHEIMER'S DISEASE (AD)

Alzheimer's disease (AD) is the leading cause of dementia among the elderly. The development of treatments that slow or halt the disease progression have been sought to improve the quality of life for patients.

STUDY: Alzheimer's (AD). THC competitively inhibits acetylcholinesterase (AChE) and prevents AChE-induced amyloid beta-peptide (Abeta) aggregation, the key pathological marker of AD. Cannabinoids are proposed to have a role in the treatment of Alzheimer's disease (AD). (Eubanks 2006)

Eubanks LM., Rogers CJ., Beuscher AE. 4th., et al. A molecular link between the active component of marijuana and Alzheimer's disease pathology. Mol Pharm. 2006;3:773–777. [PMC Free Article] [PubMed]

STUDY: Alzheimer's (AD). THC treatment decreased severity of disturbed behavior, and this effect persisted during the placebo period in patients who had received THC. (Volicer 1997)

Volicer L., Stelly M., Morris J., McLaughlin J., Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. Int J Geriatr Psychiatry. 1997;12:913–919. [PubMed]

STUDY: Alzheimer's (AD). Compared with baseline, THC led to a reduction in nocturnal motor activity. These findings were corroborated by improvements in the Neuropsychiatric Inventory total score, as well as in subscores for agitation, aberrant motor, and nighttime behaviors; no side effects were observed. (Walther 2006)

Walther S., Mahlberg R., Eichmann U., Kunz D. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. Psychopharmacology (Berl). 2006;185:524–528. [PubMed]

IN VIVO (rodent) TRIALS: Alzheimer's (AD). Possible option for chronic brain inflammation treatment of AD. Manipulation of the endocannabinoid system with WIN-55212-2 (a Cannabis derivative) is possibly involved in the regulation of brain

inflammation and may lead to use in treatment of neurodegenerative diseases such as Alzheimer's.

Results demonstrate that the cannabinoid system within the CNS (Central Nervous System) plays a critical role in regulating autoimmune inflammation, with the CNS directly suppressing autoreactive T-cell effector function via the CB(2) receptor. (Marchalant 2007) (Maresz 2007)

Marchalant Y., Rosi S., Wenk GL. Anti-inflammatory property of the cannabinoid agonist WIN-55212-2 in a rodent model of chronic brain inflammation. Neuroscience. 2007;144:1516–1522. [PMC free article] [PubMed]

Maresz K., Pryce G., Ponomarev ED., et al. Direct suppression of CNS autoimmune inflammation via the cannabinoid receptor CB(1) on neurons and CB(2) on autoreactive T cells. Nat Med. 2007;13:492–497. [PubMed]

BIPOLAR

Bipolar affective disorder is often poorly controlled by prescribed drugs. Cannabis use is common in patients with this disorder and anecdotal reports suggest that some patients take it to alleviate symptoms of both mania and depression. (Ashton 2005)

Ashton CH., Moore PB., Gallagher P., Young AH. Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential. J Psychopharmacol. 2005;19:293–300. [PubMed]

CASE REPORTS: Bipolar use of cannabis reported improvement in symptoms. One female patient found that cannabis curbed her manic rages; others described the use of cannabis as a supplement to lithium (allowing reduced consumption) or for relief of lithium's side effects. (Grinspoon 1998)

Grinspoon L., Bakalar JB. The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. J Psychoactive Drugs. 1998;30:171–177. [PubMed]

SCHIZOPHRENIA

The effects of cannabinoids on schizophrenia are controversial. Mixed results have been obtained in studies so far. Overall, negative results have occurred with THC use, while CBD is found to be safe and well-tolerated.

STUDIES REVIEW: Psychosis. Data from experimental-psychological tests show that personality changes generated by schizophrenia progression are comparable to

psychopathological phenomenon due to THC intoxication. (Emrich 1997) (Kenchadze 2006)

Emrich HM., Leweke FM., Schneider U. Towards a cannabinoid hypothesis of schizophrenia: cognitive impairments due to dysregulation of the endogenous cannabinoid system. Pharmacol Biochem Behav. 1997;56:803–807. [PubMed]

Kenchadze VG., Chkoniia ED. Clinical features of cannabis psychosis in schizophrenia patients. Georgian Med News. 2006:55–58. [PubMed]

STUDY: Schizophrenia and cannabis abuse have fewer symptoms. Less avolition (lack of interest) and fewer apathy symptoms were detected in patients with schizophrenia and cannabis abuse than in those with no abuse. (Dubertret 2006)

Dubertret C., Bidard I., Ades J., Gorwood P. Lifetime positive symptoms in patients with schizophrenia and cannabis abuse are partially explained by co-morbid addiction. Schizophr Res. 2006;86:284–290. [PubMed]

PATIENT OBSERVATIONAL STUDY: Schizophrenia. The nonpsychoactive cannabidiol (CBD) might be beneficial in the treatment of psychosis. Alterations in endocannabinoid system may contribute to pathogenesis of schizophrenia (e.g., increased density of CB(1) receptor binding & increased levels of cerebrospinal fluid endocannabinoid anandamide). (Müller-Vahl 2008)

Müller-Vahl KR, Emrich HM. Cannabis and schizophrenia: towards a cannabinoid hypothesis of schizophrenia. Expert Rev Neurother. 2008 Jul;8(7):1037-48. doi: 10.1586/14737175.8.7.1037. [PubMed]

CASE REPORTS: Schizophrenia with CBD. Open case reports of schizophrenic patients treated with cannabidiol (CBD) and a preliminary report of a controlled clinical trial comparing CBD with an atypical antipsychotic drug have confirmed that this cannabinoid can be a safe and well-tolerated alternative treatment for schizophrenia. (Zuardi 2006)

Zuardi AW1, Crippa JA, Hallak JE, Moreira FA, Guimarães FS. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. Braz J Med Biol Res. 2006 Apr;39(4):421-9. Epub 2006 Apr 3. [PubMed]

STUDIES: CBD causes antipsychotic effects. It was found to be a safe and well-tolerated alternative treatment for schizophrenia. (Zuardi 1995) (Zuardi 2006) (Zuardi 2006)

Zuardi AW., Morais SL., Guimaraes FS., Mechoulam R. Antipsychotic effect of cannabidiol. J Clin Psychiatry. 1995;56:485–486. [PubMed]

Zuardi AW., Crippa JA., Hallak JE., Moreira FA., Guimaraes FS. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. Braz J Med Biol Res. 2006;39:421–429. [PubMed]

Zuardi AW., Hallak JE., Dursun SM., et al. Cannabidiol monotherapy for treatment-resistant schizophrenia. J Psychopharmacol. 2006;20:683–686. [PubMed]

PTSD; DEPRESSION; ANXIETY

Post-Traumatic Stress disorder (PTSD) is a term for severe psychological consequences of exposure to, or confrontation with, stressful, highly traumatic events. Cannabinoids are believed to help in such cases.

IN VIVO TRIAL: Anxiety diminished. AM404-treated animals showed decreased shock-induced reinstatement of fear. (Chhatwal 2005)

Chhatwal JP., Davis M., Maguschak KA., Ressler KJ. Enhancing cannabinoid neurotransmission augments the extinction of conditioned fear. Neuropsychopharmacology. 2005;30:516–524. [PubMed]

25-Patient double-blind STUDY: Anxiety. A single dose of nabilone (a synthetic cannabinoid resembling the natural cannabinoids) produced only mild improvement in anxiety; in a repeated-dose treatment over 28 days resulted in dramatic improvement in anxiety with the nabilone group. Side effects reported were dry mouth, dry eyes, and drowsiness. Patients did not report any of the subjective "altered state" experience of marihuana. (Glass 1980) (Fabre 1981)

Glass RM., Uhlenhuth EH., Hartel FW., Schuster CR., Fischman MW. A single dose study of nabilone, a synthetic cannabinoid. Psychopharmacology (Berl). 1980;71:137–142. [PubMed]

Fabre LF., McLendon D. The efficacy and safety of nabilone (a synthetic cannabinoid) in the treatment of anxiety. J Clin Pharmacol. 1981;21:377S–382S. [PubMed]

15-SUBJECT STUDY: Anxiety reduction with CBD. A double-blind randomized, placebo-controlled study in 15 healthy subjects shows that the disruption of prefrontal-subocritical connectivity by cannabidiol may represent neurophysiological correlates of its anxiolytic properties. (Fusar-Poli 2010)

Fusar-Poli P, Allen P, Bhattacharyya S, Crippa JA, Mechelli A, Borgwardt S, Martin-Santos R, Seal ML, O'Carrol C, Atakan Z, Zuardi AW, McGuire P. Modulation of effective connectivity during emotional processing by Delta 9-tetrahydrocannabinol and cannabidiol. Int J Neuropsychopharmacol. 2010 May;13(4):421-32. doi: 10.1017/S1461145709990617. Epub 2009 Sep 24. Arch Gen Psychiatry. 2009 Jan;66(1):95-105. doi: 10.1001/archgenpsychiatry.2008.519.

15-SUBJECT STUDY: THC or CBD and anxiety. THC increased anxiety; intoxication; sedation; psychotic effects; CBD reduced anxiety. Delta9-Tetrahydrocannabinol increased anxiety, as well as levels of intoxication, sedation, and psychotic symptoms; there was a reduction in anxiety following administration of cannabidiol in 15 healthy, English-native, right-handed men who had used cannabis 15 times or less in their life. (Fusar-Poli 2009)

Fusar-Poli P1, Crippa JA, Bhattacharyya S, Borgwardt SJ, Allen P, Martin-Santos R, Seal M, Surguladze SA, O'Carrol C, Atakan Z, Zuardi AW, McGuire PK. Distinct effects of Delta-9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Arch Gen Psychiatry. 2009 Jan;66(1):95-105. doi: 10.1001/archgenpsychiatry.2008.519. [PubMed]

ASTHMA

Asthma is a chronic disease of the respiratory system in which the airway occasionally constricts, becomes inflamed, and is lined with excessive amounts of mucus.

IN VIVO STUDY: Bronchospasms. In animal experiments, after methacholine-induced or exercise-induced bronchospasm, marijuana caused a prompt correction of the bronchospasm. (Tashkin 1975)

Tashkin DP., Shapiro BJ., Lee YE., Harper CE. Effects of smoked marijuana in experimentally induced asthma. Am Rev Respir Dis. 1975;112:377–386. [PubMed]

STUDY: Bronchodilatation in asthmatic patients. Delta 1-THC was administered in metered volumes by inhalation from an aerosol device to patients in a steady state, resulted in increased peak expiratory flow rate (PEFR) and forced expiratory volume in 1 second (FEV1) and produced bronchodilatation. The rate of onset, magnitude, and duration of the bronchodilator effect was dose related. (Hartley 1978)

Hartley JP., Nogrady SG., Seaton A. Bronchodilator effect of deltaltetrahydrocannabinol. Br J Clin Pharmacol. 1978;5:523–525. [PMC free article] [PubMed]

STUDY: Asthma. In a double blind study, ten volunteer inpatient asthmatics in a steady state were given a single inhalation of a respiratory aerosol unit on three consecutive days. Before, and for one hour after treatment the pulse, blood pressure (lying and standing), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), peak flow rate (PFR), and self-rating mood scales (SRMS) were recorded. Results showed significant ventilator function improvement. The mode of action of THC differed

from that of sympathomimetic drugs and may make a suitable adjuvant in the treatment of selected asthmatics. (Williams 1976)

Williams SJ., Hartley JP., Graham JD. Bronchodilator effect of deltaltetrahydrocannabinol administered by aerosol of asthmatic patients. Thorax. 1976;31:720–723. [PMC free article] [PubMed]

CARDIO-VASCULAR DISORDERS

STUDY: Cardiac performance. The data suggests that THC acts to induce sympathetic stimulation and parasympathetic inhibition of cardiovascular control pathways. (Benowitz 1979)

Benowitz NL., Rosenberg J., Rogers W., Bachman J., Jones RT. Cardiovascular effects of intravenous delta-9-tetrahydrocannabinol: autonomic nervous mechanisms. Clin Pharmacol Ther. 1979;25:440–446. [PubMed]

STUDY: Cardiac performance. Acute THC significantly increased heart rate, shortened pre-ejection period (PEP) and prolonged left ventricular ejection time (LVETc) without any change in afterload. These findings suggest that delta-9-THC enhanced cardiac performance. (Kanakis 1976)

Kanakis C., Jr., Pouget JM., Rosen KM. The effects of delta-9-tetrahydrocannabinol (cannabis) on cardiac performance with and without beta blockade. Circulation. 1976;53:703–707. [PubMed]

CONTRASTING STUDY: Cardiac Performance. Following the smoking of 1-3 marijuana cigarettes, the heart rate rose, cardiac output rose, stroke volume, ejection fraction, PEP and LVET did not change; thus, in long-term heavy users of cannabis, marijuana has no significant effect on myocardial contractility independent of its effect on heart rate. (Tashkin 1977)

Tashkin DP., Levisman JA., Abbasi AS., Shapiro BJ., Ellis NM. Short-term effects of smoked marihuana on left ventricular function in man. Chest. 1977;72:20–26. [PubMed]

STUDY: Cardiac Performance. Cardiovascular effects of acute THC administration included increased sympathetic and reduced parasympathetic tone; supine (lying down, face up) tachycardia and increased blood pressure with upright hypotension were observed. With repetitive dosing supine bradycardia and decreased blood pressure with tolerance to orthostatic hypotension were observed. (Benowitz 1975) (Benowitz 1981)

Benowitz NL., Jones RT. Cardiovascular effects of prolonged delta-9tetrahydrocannabinol ingestion. Clin Pharmacol Ther. 1975;18:287–297. [PubMed]

Benowitz NL., Jones RT. Cardiovascular and metabolic considerations in prolonged cannabinoid administration in man. J Clin Pharmacol. 1981;21:214S–223S. [PubMed]

ATHERSCLEROSIS

Atherosclerosis is a condition in which an artery wall thickens as a result of the accumulation of fatty materials with chronic inflammation. It is the primary cause of heart disease and stroke in Western countries.

IN VIVO (mice) Model Trials: Atherosclerosis. Oral treatment with a low dose of THC inhibits atherosclerosis progression in an apolipoprotein E knockout mouse model, through pleiotropic immunomodulatory effects on lymphoid and myeloid cells. Thus, THC may be a valuable for treating atherosclerosis. (Steffens 2005)

Steffens S., Veillard NR., Arnaud C., et al. Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice. Nature. 2005;434:782–786. [PubMed]

CLINICAL DATA REVIEW: Anti-inflammatory and Analgesic observations. N-palmitoyl-ethanolamine is an endogenous endocannabinoid-like (similar as that found in the body) compound. Its concentrations are significantly increased in three different inflammatory and neuropathic conditions. The enhanced levels may possibly be related to a protective local anti-inflammatory and analgesic action. (Darmani 2005)

Darmani NA., Izzo AA., Degenhardt B., et al. Involvement of the cannabimimetic compound, N-palmitoyl-ethanolamine, in inflammatory and neuropathic conditions: Review of the available pre-clinical data, and first human studies. Neuropharmacology. 2005;48:1154–1163. [PubMed]

IN VIVO (mice) STUDY: Diabetic complications and Atherosclerosis. CBD has been shown to exert potent anti-inflammatory and antioxidant effects. It has recently been reported to lower the incidence of diabetes in nonobese diabetic mice and to preserve the blood-retinal barrier in experimental diabetes. Since a disruption of the endothelial function and integrity by HG is a crucial early event underlying the development of various diabetic complications, our results suggest that CBD, which has recently been approved for the treatment of inflammation, pain, and spasticity associated with multiple sclerosis in humans, may have significant therapeutic benefits against diabetic complications and atherosclerosis. (Rajesh 2007)

Rajesh M., Mukhopadhyay P., Batkai S., et al. Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption. Am J Physiol Heart Ore Physiol. 2007;293:H909–H918. [PMC free article] [PubMed]

GLAUCOMA

A number of studies suggest that there is a correlation, though not necessarily causal relationship, between glaucoma and systemic high blood pressure (hypertension). Ocular hypertension (OHT) refers to any situation in which intraocular pressure is higher than normal, and is the most important risk factor for glaucoma.

IN VIVO (rabbits) STUDY: Intraocular pressure. THC, CBN, and nabilone were active in lowering intraocular pressure (IOP) in rabbits, while CBD was inactive. (Eisohly 1981)

Eisohly MA., Harland E., Murphy JC., Wirth P., Waller CW. Cannabinoids in glaucoma: a primary screening procedure. J Clin Pharmacol. 1981;21:472S–478S. [PubMed]

IN VIVO (rabbits) STUDY: Intraocular pressure. Thirty-two different cannabinoids (including delta 9- and delta 8-THC derivatives and metabolites, other natural and synthetic cannabinoids, and some non-cannabinoid constituents of Cannabis) were tested for their ability to reduce intraocular pressure (IOP) in the rabbit. The data revealed that certain derivatives of THC were more active in lowering IOP than the parent cannabinoids. (ElSohly 1984)

ElSohly MA., Harland EC., Benigni DA., Waller CW. Cannabinoids in glaucoma II: the effect of different cannabinoids on intraocular pressure of the rabbit. Curr Eye Res. 1984;3:841–850. [PubMed]

IN VIVO (rabbit) STUDY: Intraocular pressure. Topical administration of anandamide and arachidonyl propionitrileamide decreased IOP; rimonabant antagonized the IOP reduction, suggesting that cannabinoids lower IOP through CB1 receptors. (Laine 2002) (Pate 1995)

Laine K., Jarvinen K., Pate DW., Urtti A., Jarvinen T. Effect of the enzyme inhibitor, phenylmethylsulfonyl fluoride, on the IOP profiles of topical anandamides. Invest Ophthalmol Vis Sci. 2002;43:393–397. [PubMed]

Pate DW., Jarvinen K., Urtti A., Jarho P., Jarvinen T. Ophthalmic arachidonylethanolamide decreases intraocular pressure in normotensive rabbits. Curr Eye Res. 1995;14:791–797. [PubMed]

IN VIVO (rabbit) STUDY: Intraocular pressure with implications regarding glaucoma treatment. Significantly, higher levels of CB1 mRNA levels were found in the ciliary body than in the iris, retina, and choroid. CB2 mRNA was undetectable. This expression pattern supports a specific role for the CB1 receptor in controlling IOP. (Porcella 1998)

Porcella A., Casellas P., Gessa GL., Pani L. Cannabinoid receptor CB1 mRNA is highly expressed in the rat ciliary body: implications for the antiglaucoma properties of marihuana. Brain Res Mol Brain Res. 1998;58:240–245. [PubMed]

IN VIVO (cat) STUDIES: Intraocular pressure (IOP). Whole marijuana extract, THC and other plant cannabinoids reduced IOP when delivered topically to cat eyes with osmotic minipumps. Ocular toxicity was not apparent during administration of plant cannabinoids except for: After THC treatment, conjunctival erythema and chemosis as well as corneal opacification occured. Although these changes also appeared with marijuana extract, their intensity was much reduced. (Colasanti 1984) (Colasanti 1984) (Colasanti 1984)

Colasanti BK., Brown RE., Craig CR. Ocular hypotension, ocular toxicity, and neurotoxicity in response to marihuana extract and cannabidiol. Gen Pharmacol. 1984;15:479–484. [PubMed]

Colasanti BK., Craig CR., Allara RD. Intraocular pressure, ocular toxicity and neurotoxicity after administration of cannabinol or cannabigerol. Exp Eye Res. 1984;39:251–259. [PubMed]

Colasanti BK., Powell SR., Craig CR. Intraocular pressure, ocular toxicity and neurotoxicity after administration of delta 9-tetrahydrocannabinol or cannabichromene. Exp Eye Res. 1984;38:63–71. [PubMed]

HUMAN OBSERVATIONAL STUDIES: Intraocular pressure reduction. Marijuana smoking was shown to reduce IOP as early as 1971; the effect was later confirmed. (Hepler 1971) (Merritt 1981) (Merritt 1981) (Merritt 1980)

Hepler RS., Frank IR. Marihuana smoking and intraocular pressure. Jama. 1971;217:1392. [PubMed]

Merritt JC., Olsen JL., Armstrong JR., McKinnon SM. Topical delta 9-tetrahydrocannabinol in hypertensive glaucomas. J Pharm Pharmacol. 1981;33:40–41. [PubMed]

Merritt JC., Perry DD., Russell DN., Jones BF. Topical delta 9-tetrahydrocannabinol and aqueous dynamics in glaucoma. J Clin Pharmacol. 1981;21:467S–471S. [PubMed]

Merritt JC., Crawford WJ., Alexander PC., Anduze AL., Gelbart SS. Effect of marihuana on intraocular and blood pressure in glaucoma. Ophthalmology. 1980;87:222–228. [PubMed]

2-Volunteer STUDY REPORT: Intraocular pressure reduction. As indicated by the subjects' report of degree of "high," the peak effect of THC on the central nervous system coincided well with the reduction in intraocular pressure induced by the drug. However, hypotonia (reduction) outlasted euphoria. The results indicate that THC may have value as a hypotonizing ocular drug. (Purnell 1975)

PurneII WD., Gregg JM. DeIta(9)-tetrahydrocannabinoI, euphoria and intraocular pressure in man. Ann Ophthalmol. 1975;7:921–923. [PubMed]

HUMAN CLINICAL STUDIES: Intraocular pressure reduction. The functional responses after THC inhalation in sitting normotensive and hypertensive patients included

invariable increases in heart rate followed by substantial decreases in systolic pressure, diastolic pressure, and intraocular pressure. The intensity and duration (3-4 hours) of the arterial and ocular pressure responses to THC were greater in hypertensives than in normotensive patients. The salient observation after THC inhalation was that the changes in ocular pressure paralleled the changes in blood pressure in each glaucoma patient. (Crawford 1979)

Crawford WJ., Merritt JC. Effects of tetrahydrocannabinol on arterial and intraocular hypertension. IntJ Clin Pharmacol Biopharm. 1979;17:191–196. [PubMed]

STUDY: Intraocular pressure (IOP) reduction. A single sublingual dose of THC, but not cannabidiol, reduced the IOP temporarily and was well tolerated by most patients. (Tomida 2006)

Tomida I., Azuara-Blanco A., House H., Flint M., Pertwee RG., Robson PJ. Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study. J Glaucoma. 2006;15:349–353. [PubMed]

CANCER

Cancer is characterized by an uncontrolled proliferation of cells, along with the ability of those cells to spread and invade other tissues. Cannabinoid's ability to attack cancer cells was noticed in the 1970s and scientists have been actively studying cannabis and the many ways it interferes and stops cancer progression, ever since.
Anti-cancer agents affect cancer cells through direct apoptosis (cell death), by damaging cancer cell DNA, or by interrupting the cancer cell cycle pathways. A major discovery in cannabinoid use for cancer treatment was its ability to target and kill tumor cells. The majority of effects of cannabinoids are mediated via CB1 and CB2 receptor activation, which then affects the regulation of key cell signaling pathways that are involved in cancer cell survival, invasion, angiogenesis (blood supply), energy metabolism, growth, immune environment, metastasis (spread and relocation), etc.

Several preclinical studies suggest that Δ9-THC and other naturally occurring cannabinoids, synthetic cannabinoid agonists (activators) and endocannabinoids have anti-cancer effects in vitro against lung carcinoma, gliomas (brain), thyroid epithelioma, lymphoma, skin carcinoma, uterine carcinoma, breast cancer, prostate carcinoma, pancreatic cancer and neuroblastoma. These findings are also supported by in vivo studies.

It's important to note that the palliative effects of cannabinoids substantially increase the cancer patient's quality of life. These include inhibition of nausea and emesis which are associated with chemo- or radiotherapy, appetite stimulation, pain relief, mood elevation and relief from insomnia. Science and governments are beginning to acknowledge the benefits of cannabinoids. Synthetic THC (Marinol, Dronabinol) and its

derivative nabilone (Cesamet), as well as Sativex, have been approved in several countries to control nausea and cancer-related pain in cancer patients undergoing chemotherapy.

A major challenge for the case of using cannabinoids for health therapy is the development of safe and effective methods that lead to therapeutic effects but avoid adverse psychoactive effects.

Chakravarti B, Ravi J, Ganju RK. Cannabinoids as therapeutic agents in cancer: current status and future implications. Onco. 2014 Aug 15;5(15):5852-72. [PubMed] [Free PMC Article] - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4171598/

Cancer Studies Overview
Breast Cancer
Prostate Cancer
Lung Cancer
Skin Cancer
Pancreatic Cancer
Bone Cancer
Leukemia
Glioma
Lymphoma
Oral Cancer
Head and Neck Cancer
Thyroid Carcinoma

CANCER STUDIES OVERVIEW

REVIEW of IN VITRO and INVO Literature: Tumor cell growth reduction. Cannabinoids have been licensed for clinical use as palliative treatment of chemotherapy, but further evidence showed direct antiproliferative actions of cannabinoid agonists on several tumor cells in vitro and in animal models. (Bifulco 2006)

Bifulco M, Laezza C, Pisanti S, Gazzerro P. Cannabinoids and cancer: pros and cons of an antitumour strategy. Br J Pharmacol. 2006 May;148(2):123-35. [PubMed] [Free PMC Article]

REVIEW: Encannabinoids and Cancer. Modulation of the endocannabinoid system by pharmacological agents in various cancer types reveals that it can mediate antiproliferative and apoptotic effects by both cannabinoid receptor-dependent and -independent pathways. Selective agonists and antagonists of the cannabinoid receptors, inhibitors of endocannabinoid hydrolysis, and cannabinoid analogs have

been utilized to probe the pathways involved in the effects of the endocannabinoid system on cancer cell apoptosis, proliferation, migration, adhesion, and invasion. The antiproliferative and apoptotic effects produced by some of these pharmacological probes reveal that the endocannabinoid system is a promising new target for the development of novel chemotherapeutics to treat cancer. (Hermanson 2011)

Hermanson, Daniel J. and Lawrence J. Marnett. Cannabinoids, Endocannabinoids and Cancer. Cancer Metastasis Rev. Dec 2011; 30(3-4): 599–612. doi: 10.1007/s10555-011-9318-8 [PubMed] [Free Article]

REVIEW: Suppression of angiogenesis and metastasis. Cannabinoids have been reported to inhibit angiogenesis (blood supply), cell migration and metastasis (spread) in different types of cancer, pointing to a potential role of the endocannabinoid system as a target for a therapeutic approach of such malignant diseases. The potential use of cannabinoids to retard tumor growth and spreading is even more appealing considering that they show a good safety profile, regarding toxicity, and are already used in cancer patients as palliatives to stimulate appetite and to prevent devastating effects such as nausea, vomiting and pain. Cannabinoids were also found to be suppressors of tumor invasion. (Bifulco 2007)

Bifulco M., Laezza C., Gazzerro P., Pentimalli F. Endocannabinoids as emerging suppressors of angiogenesis and tumor invasion (review). Oncol Rep. 2007;17:813–816. [PubMed]

STUDY REVIEW: Lung, Breast and Glioma Cancers and cannabinoids. In 1975, Munson discovered that cannabinoids suppress Lewis lung carcinoma cell growth. The mechanism of this action was shown to be inhibition of DNA synthesis. Antiproliferative action on some other cancer cells was also found. Di Marzo's group found that cannabinoids inhibit breast cancer cell proliferation, and Guzman's group found that cannabinoids inhibit the growth of C6 glioma cell. Other groups also started work in this field, and today, a wide array of cancer cell lines that are affected is known. (Hall 2005) (Kogan 2005)

Hall W., Christie M., Currow D. Cannabinoids and cancer: causation, remediation, and palliation. Lancet Oncol. 2005;6:35–42. [PubMed]

Kogan NM. Cannabinoids and cancer. Mini Rev Med Chem. 2005;5:941–952. [PubMed]

BREAST CANCER

Breast cancer is one of the most common human malignancies and the second leading cause of cancer-related deaths in women, and its incidence in the developing world is on the rise. It represents approximately 30% of newly diagnosed cancers each

year. It is mainly classified into three main subtypes according to their molecular profiles: hormone receptor-positive, HER2-positive (ErbB2-positive, a member of EGFR family) and triple-negative tumors. Cannabinoid-based medicines have been useful for the treatment of all three breast cancer subtypes.

STUDY: Breast cancer. The endocannabinoid system has been shown to modulate key cell-signaling pathways involved in cancer cell growth. In this study, it was shown that cannabinoid receptor type 1 (CB1) antagonist (blocker) Rimonabant (SR141716) inhibited human breast cancer cell proliferation, being more effective in highly invasive metastatic MDA-MB-231 cells than in less-invasive T47D and MCF-7 cells. SR141716 inhibits human breast cancer cell growth via a CB1 receptor lipid raft/caveolae-mediated mechanism. (Sarnataro 2006)

Sarnataro D., Pisanti S., Santoro A., et al. The cannabinoid CB1 receptor antagonist rimonabant (SR141716) inhibits human breast cancer cell proliferation through a lipid raft-mediated mechanism. Mol Pharmacol. 2006;70:1298–1306. [PubMed]

STUDIES: Breast Cancer growth and invasion. Cannabinoids modulate the growth of hormone sensitive breast cancer cells. JWH-O15 inhibits hormone sensitive breast cancer metastasis by modulating CXCL12/CXCR4 signaling axis. (Nasser 2011) (Zlotnik 2011)

Nasser MW, Qamri Z, Deol YS, Smith D, Shilo K, Zou X, Ganju RK. Crosstalk between chemokine receptor CXCR4 and cannabinoid receptor CB2 in modulating breast cancer growth and invasion. PLoS One. 2011;6(9):e23901. [PMC free article] [PubMed]

Zlotnik A, Burkhardt AM, Homey B. Homeostatic chemokine receptors and organ-specific metastasis. Nat Rev Immunol. 2011;11(9):597–606. [PubMed]

STUDY: Breast Cancer. Endocannabinoids such as anandamide (AEA) are important lipid ligands (receptor binders) regulating cell proliferation, differentiation and apoptosis. Their levels are regulated by hydrolase enzymes, the fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL). Breast tumor cells express FAAH abundantly. Inhibition of FAAH (siRNA-FAAH or FAAH inhibitor URB597) induced cancer cell death. (Ranger 2009)

Ranger JJ, Levy DE, Shahalizadeh S, Hallett M, Muller WJ. Identification of a Stat3-dependent transcription regulatory network involved in metastatic progression. Cancer Res. 2009;69(17):6823–6830. [PMC free article] [PubMed]

STUDIES: Breast cancer growth. Anandamide inhibits basal and nerve growth factor (NGF) induced proliferation of MCF-7 and EFM-19 cells in culture through CB1 receptor. (Melck 2000) (DePetrocellis 1998) (Melck 1998)

Melck D, De Petrocellis L, Orlando P, Bisogno T, Laezza C, Bifulco M, Di Marzo V. Suppression of nerve growth factor Trk receptors and prolactin receptors by endocannabinoids leads to inhibition of human breast and prostate cancer cell proliferation. Endocrinology. 2000;141(1):118–126. [PubMed]

De Petrocellis L, Melck D, Palmisano A, Bisogno T, Laezza C, Bifulco M, Di Marzo V. The endogenous cannabinoid anandamide inhibits human breast cancer cell proliferation. Proc Natl Acad Sci U S A. 1998;95(14):8375–8380. [PMC free article] [PubMed]

Melck D, Rueda D, Galve-Roperh I, De Petrocellis L, Guzman M, Di Marzo V. Involvement of the cAMP/protein kinase A pathway and of mitogen-activated protein kinase in the anti-proliferative effects of anandamide in human breast cancer cells. FEBS Lett. 1999;463(3):235–240. [PubMed]

STUDY: Breast cancer cells. THC, through activation of CB2 cannabinoid receptors, reduced human breast cancer cell proliferation by blocking the progression of the cell cycle and by inducing apoptosis. THC arrested cells in G2M via downregulation of Cdc2. (Caffarel 2006)

Caffarel MM., Sarrio D., Palacios J., Guzman M., Sanchez C. Delta9-tetrahydrocannabinol inhibits cell cycle progression in human breast cancer cells through Cdc2 regulation. Cancer Res. 2006;66:6615–6621. [PubMed]

STUDY: Breast Cancer and Delta-9 THC. Delta-9 THC inhibits 17beta-estradiol-induced proliferation of ER^-/PR^+ breast cancer cells. This study shows the mechanism of Delta(9)-tetrahydrocannabinol (THC) antiproliferative action in these cells, and shows that it activates the transcription factor JunD that leads to apoptosis in ER^-/PR^+ breast cancer cells. Data collected in the study shows not only that cannabinoids regulate JunD but, more generally, that JunD activation reduces the proliferation of cancer cells, which points to a new target to inhibit breast cancer progression. (vonBueren 2008) (Caffarel 2008)

von Bueren AO, Schlumpf M, Lichtensteiger W. Delta(9)-tetrahydrocannabinol inhibits 17beta-estradiol-induced proliferation and fails to activate androgen and estrogen receptors in MCF7 human breast cancer cells. Anticancer Res. 2008;28(1A):85–89. [PubMed]

Caffarel MM, Moreno-Bueno G, Cerutti C, Palacios J, Guzman M, Mechta-Grigoriou F, Sanchez C. JunD is involved in the antiproliferative effect of Delta9-tetrahydrocannabinol on human breast cancer cells. Oncogene. 2008 Aug 28;27(37):5033-44. doi: 10.1038/onc.2008.145. Epub 2008 May 5. [PubMed]

STUDY: Breast cancer. Anandamide inhibits adenylyl cyclase (AC), thus activating the Raf-1/ERK/MAP pathway in ER^+/PR^+ breast cancer cells and leading to cell cycle arrest and apoptotic cell death. The analog of anandamide, Met-F-AEA reduces MDA-MB-231 proliferation by arresting cells in the S phase of the cell cycle. (DePetrocellis 1998)

De Petrocellis L, Melck D, Palmisano A, Bisogno T, Laezza C, Bifulco M, Di Marzo V. The endogenous cannabinoid anandamide inhibits human breast cancer cell proliferation. Proc Natl Acad Sci U S A. 1998;95(14):8375–8380. [PMC free article] [PubMed]

STUDY: Breast cancer. Study shows that anandamide inhibits proliferation of MDA-MB31 cells by modulating Wnt/β-catenin signaling pathway. This effect occurred by inhibition of the cyclin-dependent kinase CDK2. (Grimaldi 2006) (Laezza 2006) (Laezza 2013)

Grimaldi C, Pisanti S, Laezza C, Malfitano AM, Santoro A, Vitale M, Caruso MG, Notarnicola M, Iacuzzo I, Portella G, Di Marzo V, Bifulco M. Anandamide inhibits adhesion and migration of breast cancer cells. Exp Cell Res. 2006;312(4):363–373. [PubMed]

Laezza C, Pisanti S, Crescenzi E, Bifulco M. Anandamide inhibits Cdk2 and activates Chk1 leading to cell cycle arrest in human breast cancer cells. FEBS Lett. 2006;580(26):6076–6082. [PubMed]

Laezza C, d'Alessandro A, Malfitano AM, Bifulco M. Anandamide inhibits the Wnt/beta-catenin signalling pathway in human breast cancer MDA MB 231 cells. Eur J Cancer. 2013;49(8):2066–2067. [PubMed]

STUDY: Breast cancer. WIN 55,212-2 and JWH-133 produce an inhibition of MDA-MB-231 proliferation by blocking the progression through the cell cycle, G1 to S phase transition and induced apoptosis. The anti-proliferative effect of WIN 55,212-2 and JWH-133 is validated in both in xenograft-based and PyMT genetically engineered model of triple-negative breast cancer modulate through the COX-2/PGE2 signaling pathway. JWH-015 also reduces breast cancer-induced bone pain, bone loss, and breast cancer proliferation via cytokine/chemokine suppression. (Qamri 2009)

Qamri Z, Preet A, Nasser MW, Bass CE, Leone G, Barsky SH, Ganju RK. Synthetic cannabinoid receptor agonists inhibit tumor growth and metastasis of breast cancer. Mol Cancer Ther. 2009;8(11):3117–3129. [PMC free article] [PubMed]

STUDY: Breast cancer. Cannabidiol (CBD) induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy (self-digestion). CBD inhibits AKT and mTOR signaling as well as decreased levels of phosphorylated mTOR and 4EBP1, and cyclin D1. CBD enhances the interaction between beclin1 and Vps34; it inhibits the association between beclin1 and Bcl-2. (Shrivastava 2011)

Shrivastava A, Kuzontkoski PM, Groopman JE, Prasad A. Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy. Mol Cancer Ther. 2011;10(7):1161–1172. [PubMed]

STUDY: Breast cancer. Increased circulating levels of L-alpha-lysophosphatidylinositol (LPI) are associated with cancer, including enhanced breast cancer cell migration, orientation and polarization. LPI is a potent, ligand (receptor binder) for the G-protein-coupled receptor GPR55. CBD blocks this effect, representing a chemopreventive tool for the treatment of breast cancer. (Ford 2010)

Ford LA, Roelofs AJ, Anavi-Goffer S, Mowat L, Simpson DG, Irving AJ, Rogers MJ, Rajnicek AM, Ross RA. A role for L-alpha-lysophosphatidylinositol and GPR55 in the modulation of migration, orientation and polarization of human breast cancer cells. Br J Pharmacol. 2010;160(3):762–771. [PMC free article] [PubMed]

PROSTATE CANCER

Prostate cancer is the most common malignancy among men of all races and is one of the leading causes of cancer death in this population.

Prostate cancer research involves CB1 and CB2 expression (levels are higher in prostate cancer tissues), the cannabinoid receptor GPR55 (expressed in PC-3 and DU-145 cells), and several cell lines including PC-3, DU-145, LNCaP, CWR22Rv1, CA-HPV-10 as compared with normal prostate epithelial cells.

Δ9 –THC, WIN-55,212-2, R(+)-Methanandamide, Cannabidiol (CBD), Anandamide, JWH-015, HU120, 2-AG and its stable analogue noladin have exerted anti-proliferative, apoptotic and anti-invasive effects in different prostate cancer cells both in vitro and in vivo.

STUDY: Prostate cancer. Δ9 –THC induced apoptosis via a receptor-independent manner. In another study, the same group reported that activation of cannabinoid receptors in PC-3 cells stimulated the PI3K/Akt pathway with sequential involvement of Raf-1/ERK1/2 and nerve growth factor induction. (Ruiz 1999) (Nithipatikom 2004)

Ruiz L, Miguel A, Diaz-Laviada I. Delta9-tetrahydrocannabinol induces apoptosis in human prostate PC-3 cells via a receptor-independent mechanism. FEBS Lett. 1999;458(3):400–404. [PubMed]

Nithipatikom K, Endsley MP, Isbell MA, Falck JR, Iwamoto Y, Hillard CJ, Campbell WB. 2-arachidonoylglycerol: a novel inhibitor of androgen-independent prostate cancer cell invasion. Cancer Res. 2004;64(24):8826–8830. [PubMed]

STUDY: Prostate cancer. Cannabinoid-induced apoptosis of human prostate cancer cells LNCaP proceeded through sustained activation of ERK1/2 leading to G1 cell cycle arrest. WIN-55,212-2 also mimicked the same effect in LNCaP cells as CBD. (Sarfaraz 2006) (Sreevalsan 2011)

Sarfaraz S., Afaq F., Adhami VM., Malik A., Mukhtar H. Cannabinoid receptor agonist-induced apoptosis of human prostate cancer cells LNCaP proceeds through sustained activation of ERK1/2 leading to G1 cell cycle arrest. J Biol Chem. 2006;281:39480–39491. [PubMed]

Sreevalsan S, Joseph S, Jutooru I, Chadalapaka G, Safe SH. Induction of apoptosis by cannabinoids in prostate and colon cancer cells is phosphatase dependent. Anticancer Res. Nov 2011;31(11):3799–3807. [PMC free article] [PubMed]

STUDY: Prostate cancer. Anandamide (ANA) induced a decrease of EGFR levels on LNCaP, DU145, and PC3 prostatic cancer cells by acting through cannabinoid CB1 receptor subtype and this lead to an inhibition of the EGF-stimulated growth of these cells. Moreover, the G1 arrest of metastatic DU145 and PC3 growth was accompanied by a massive cell death by apoptosis and/or necrosis (Mimeault 2003)

Mimeault M, Pommery N, Wattez N, Bailly C, Henichart JP. Anti-proliferative and apoptotic effects of anandamide in human prostatic cancer cell lines: implication of epidermal growth factor receptor down-regulation and ceramide production. Prostate. 2003;56(1):1–12. [PubMed]

STUDY: Prostate cancer. JWH-015 triggered a de novo synthesis of ceramide, which induced cell death, followed by JNK (c-Jun N-terminal kinase) activation and Akt inhibition. (Olea-Herrero 2009)

Olea-Herrero N, Vara D, Malagarie-Cazenave S, Diaz-Laviada I. Inhibition of human tumor prostate PC-3 cell growth by cannabinoids R(+)-Methanandamide and JWH-015: involvement of CB2. Br J Cancer. 2009;101(6):940–950. [PMC free article] [PubMed]

STUDY: Prostate cancer. Effects of R(+)-Methanandamide and JWH-015 were rescued by treatment with SR 144528 in PC-3 cells. Findings suggest that CB2 agonists may treat prostate cancer by decreasing cancer epithelial cell proliferation. (Olea-Herrero 2009) (Olea-Herrero 2009)

Olea-Herrero N, Vara D, Malagarie-Cazenave S, Diaz-Laviada I. Inhibition of human tumour prostate PC-3 cell growth by cannabinoids R(+)-Methanandamide and JWH-015: involvement of CB2. Br J Cancer. 2009;101(6):940–950. [PMC free article] [PubMed]

Olea-Herrero N, Vara D, Malagarie-Cazenave S, Diaz-Laviada I. The cannabinoid R+ methanandamide induces IL-6 secretion by prostate cancer PC3 cells. J Immunotoxicol. 2009;6(4):249–256. [PubMed]

STUDY: Prostate cancer. (R)-methanandamide was shown to have a mitogenic effect (induces mitosis) on LNCaP cells at very low doses. (Sanchez 2003)

Sanchez MG, Sanchez AM, Ruiz-Llorente L, Diaz-Laviada I. Enhancement of androgen receptor expression induced by (R)-methanandamide in prostate LNCaP cells. FEBS Lett. 2003;555(3):561–566. [PubMed]

STUDY: Prostate cancer. FAAH is a serine hydrolase that metabolizes N-acylethanolamines including AEA, OEA and PEA to fatty acids plus ethanolamine. A recent report showed that FAAH is also over-expressed in prostate cancer cells and the inhibition of FAAH can enhance the survival of cancer patient. (Cravatt 1996) (Cravatt 2001)

Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature. 1996;384(6604):83–87. [PubMed]

Cravatt BF, Demarest K, Patricelli MP, Bracey MH, Giang DK, Martin BR, Lichtman AH. Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling

in mice lacking fatty acid amide hydrolase. Proc Natl Acad Sci U S A. 2001;98(16):9371–9376. [PMC free article] [PubMed]

LUNG CANCER

Lung cancer has one of the highest mortality rates among cancer-suffering patients. Cannabinoids could halt tumor development without side effects via specific targeting of CB1/CB2 receptors.

STUDIES. Lung Cancer. Studies suggest the involvement of COX-2 and PPAR-γ in CBD's proapoptotic and tumor-regressive action in A549, H460 cells and primary cells from a patient with lung cancer. Moreover, CBD caused up-regulation of COX-2 and PPAR-γ in tumor tissue and tumor regression in A549-xenografted nude mice. (Ramer 2013)

Ramer R, Heinemann K, Merkord J, Rohde H, Salamon A, Linnebacher M, Hinz B. COX-2 and PPAR-gamma confer cannabidiol-induced apoptosis of human lung cancer cells. Mol Cancer Ther. 2013;12(1):69–82. [PubMed]

IN VITRO STUDY: Lung cancer. JWH-133 induced anti-proliferative and anti-angiogenic potential in A549 cell line via DNA fragmentation. (Vidinsky 2012)

Vidinsky B, Gal P, Pilatova M, Vidova Z, Solar P, Varinska L, Ivanova L, Mojzis J. Anti-proliferative and anti-angiogenic effects of CB2R agonist (JWH-133) in non-small lung cancer cells (A549) and human umbilical vein endothelial cells: an in vitro investigation. Folia Biol (Praha) 2012;58(2):75–80. [PubMed]

STUDY: Lung cancer. The role of FAAH in regulating the effects of AEA in NSCLC has been shown. Blocking FAAH increases the levels of AEA, which in turn inhibits EGFR signaling pathway, ultimately leading to cell cycle arrest and apoptosis. (Ravi 2014)

Ravi J, Sneh A, Shilo K, Nasser MW, Ganju RK. FAAH inhibition enhances anandamide mediated anti-tumorigenic effects in non-small cell lung cancer by downregulating the EGF/EGFR pathway. Oncotarget. 2014;5(9):2475–2486. [PMC free article] [PubMed]

SKIN CANCER

Melanoma is the main cause of skin cancer-related deaths worldwide. CB1 and CB2 receptors are expressed in normal skin and in skin tumors of mice and humans.

IN VIVO (mice) STUDY: With implications of suppressing human melanomas. Human melanomas express CB1 and CB2 cannabinoid receptors. Activation of these receptors decreased growth, proliferation, angiogenesis, and metastasis, and increased

apoptosis, of melanomas in mice by inducing the apoptotic death of tumorigenic epidermal cells, without affecting the nontransformed epidermal cells. WIN-55,212-2 or JWH-133 induced anti-proliferative effect in epidermal cell lines (PDV.C57 and HaCa4) and reduced malignant tumors. WIN-55,212-2 or JWH-133 induced G1 cell cycle arrest on melanoma cells, via inhibition of p-Akt and hypophosphorylation of the pRb retinoblastoma protein tumor suppressor. (Blazquez 2006)

Blazquez C., Carracedo A., Barrado L., et al. Cannabinoid receptors as novel targets for the treatment of melanoma. FASEB J. 2006;20:2633–2635. [PubMed]

PANCREATIC CANCER

Pancreatic cancer is one of the most aggressive and devastating human malignancies. It is characterized by anorexia, flatulence, weakness, dramatic weight loss, back pain, jaundice, recent onset of diabetes, and clay-colored stools if the pancreatic and biliary ducts are obstructed. Symptoms depend on the location of the tumor within the pancreas.

STUDY: Pancreatic cancer. CB1 and CB2 receptors were expressed in normal and pancreatic cancer tissues, analyzed by RT-PCR. Cannabinoid receptors on pancreatic cancer cells may affect prognosis and pain status of pancreatic ductal adenocarcinoma PDAC patients. (Michalski 2008)

Michalski CW, Oti FE, Erkan M, Sauliunaite D, Bergmann F, Pacher P, Batkai S, Muller MW, Giese NA, Friess H, Kleeff J. Cannabinoids in pancreatic cancer: correlation with survival and pain. Int J Cancer. 2008;122(4):742–750. [PMC free article] [PubMed]

STUDY: Pancreatic tumor cells. Cannabinoids induced apoptosis of pancreatic tumor cells via CB2 receptor and ceramide-dependent up-regulation of stress protein p8 and endoplasmic reticulum ATF-4 and TRB3 stress-related genes. These effects were prevented by blockade of the CB2 cannabinoid receptor or by pharmacologic inhibition of ceramide synthesis de novo. (Carracedo 2006)

Carracedo A., Gironella M., Lorente M., et al. Cannabinoids induce apoptosis of pancreatic tumor cells via endoplasmic reticulum stress-related genes. Cancer Res. 2006;66:6748–6755. [PubMed]

STUDY: Pancreatic cancer. CB1 receptor antagonist AM251 induced cell death in pancreatic MIAPaCa-2 cells occurred via receptor-independent manner. (Fogli 2006)

Fogli S, Nieri P, Chicca A, Adinolfi B, Mariotti V, Iacopetti P, Breschi MC, Pellegrini S. Cannabinoid derivatives induce cell death in pancreatic MIA PaCa-2 cells via a receptor-independent mechanism. FEBS Lett. 2006;580(7):1733–1739. [PubMed]

BONE CANCER

Chondrosarcoma and osteosarcoma are the most frequent bone cancers. Bone metastases are a common complication of cancer and the most frequent type of pain related to cancer. Breast cancer and prostate cancer mainly metastasize to bone which act as a fertile soil for the growth of secondary tumors. The skeletal endocannabinoid system plays a significant role in regulating bone mass and bone turnover.

STUDY: Bone cancer pain. Intraplantar (inner sole of foot) administration of AEA reduces mechanical hyperalgesia (high sensitivity to pain), URB597 increases AEA levels and decreases hyperalgesia in a model of calcaneus (heel) bone cancer pain. (Khasabova 2008)

Khasabova IA, Khasabov SG, Harding-Rose C, Coicou LG, Seybold BA, Lindberg AE, Steevens CD, Simone DA, Seybold VS. A decrease in anandamide signaling contributes to the maintenance of cutaneous mechanical hyperalgesia in a model of bone cancer pain. J Neurosci. 2008;28(44):11141–11152. [PMC free article] [PubMed]

TRIAL: Pain with advanced cancer. This multicenter, double-blind, randomized, placebo-controlled, parallel-group trial compared efficacy of Sativex, a THC:CBD combination, a THC extract, and placebo with 177 patients with cancer pain. Results showed twice as many patients taking THC:CBD had a reduction of more than 30% from baseline pain NRS score when compared with placebo. The number of THC group responders was similar to placebo. This study shows that THC:CBD combination is efficacious for relief of pain in patients with advanced cancer pain not fully relieved by strong opioids. (Johnson 2010)

Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage. 2010;39(2):167–179. [PubMed]

STUDIES: Bone cancer, neuropathic pain and bone loss. WIN55,212-2 induces apoptosis in the NCTC-2472 sarcoma cell line and AM1241 produced a reduction in bone loss in bone tumor animal model (NCTC-2472 cell line injected into femur of mice). Effects of subcutaneously administered WIN55,212-2 on weight bearing and mechanical hyperalgesia were consistent with cannabinoid receptor mediated anti-nociception. (Hald 2008) (Lozano-Ondoua 2010)

Hald A, Ding M, Egerod K, Hansen RR, Konradsen D, Jorgensen SG, Atalay B, Nasser A, Bjerrum OJ, Heegaard AM. Differential effects of repeated low dose treatment with the cannabinoid agonist WIN 55,212-2 in experimental models of bone

cancer pain and neuropathic pain. Pharmacol Biochem Behav. 2008;91(1):38–46. [PubMed]

Lozano-Ondoua AN, Wright C, Vardanyan A, King T, Largent-Milnes TM, Nelson M, Jimenez-Andrade JM, Mantyh PW, Vanderah TW. A cannabinoid 2 receptor agonist attenuates bone cancer-induced pain and bone loss. Life Sci. 2010;86(17-18):646–653. [PMC free article] [PubMed]

STUDY: Bone cancer and pain. WIN55,212-2 attenuates tumor-evoked mechanical hyperalgesia following local (intraplantar) administration through activation of CB1 and CB2 receptors. (Potenzieri 2008)

Potenzieri C, Harding-Rose C, Simone DA. The cannabinoid receptor agonist, WIN 55, 212-2, attenuates tumor-evoked hyperalgesia through peripheral mechanisms. Brain Res. 2008;1215:69–75. [PMC free article] [PubMed]

STUDY: Bone tumor pain. Injection of CP55 940 produced anti-nociceptive properties in the tail flick test and suppressed mechanical hyperalgesia in NCTC-2472 or melanoma B16-F10 xenografted bone tumor model. (Hamamoto 2007)

Hamamoto DT, Giridharagopalan S, Simone DA. Acute and chronic administration of the cannabinoid receptor agonist CP 55,940 attenuates tumor-evoked hyperalgesia. Eur J Pharmacol. 2007;558(1-3):73–87. [PMC free article] [PubMed]

STUDY: Bone cancer pain. Intrathecal (brain or spinal cord) administration of either URB597 or MGL (URB602) inhibitors failed to produce anti-nociception when tested for spontaneous flinches, limb use and weight bearing. Moreover, the CB1 agonist arachidonoyl-2-chloroethylamide (ACEA) produces anti–nociceptive properties following intrathecal administration in this model; ACEA suppressed spontaneous flinches and increased limb use and weight bearing.

Furuse S, Kawamata T, Yamamoto J, Niiyama Y, Omote K, Watanabe M, Namiki A. Reduction of bone cancer pain by activation of spinal cannabinoid receptor 1 and its expression in the superficial dorsal horn of the spinal cord in a murine model of bone cancer pain. Anesthesiology. 2009;111(1):173–186. [PubMed]

STUDY: Bone cancer pain. AM1241 produces significantly reduced bone loss and decreased the incidence of cancer-induced bone fractures. Administration of JWH-015 and AM1241 attenuated tumor-evoked tactile allodynia and thermal hyperalgesia by reducing NR2B-dependent activity. (Curto-Reyes 2010) (Gu 2011)

Curto-Reyes V, Llames S, Hidalgo A, Menendez L, Baamonde A. Spinal and peripheral analgesic effects of the CB2 cannabinoid receptor agonist AM1241 in two models of bone cancer-induced pain. Br J Pharmacol. 2010;160(3):561–573. [PMC free article] [PubMed]

Gu X, Mei F, Liu Y, Zhang R, Zhang J, Ma Z. Intrathecal administration of the cannabinoid 2 receptor agonist JWH015 can attenuate cancer pain and decrease mRNA expression of the 2B subunit of N-methyl-D-aspartic acid. Anesth Analg. 2011;113(2):405–411. [PubMed]

STUDY: Bone pain. CB2 agonist, JWH-015 reduced breast cancer induced bone pain, bone loss, and breast cancer cell proliferation via cytokine/chemokine suppression in murine mammary cell line implanted into the femur intramedullary space. JWH-015 increased survival without the major side effects of current therapeutic options. (Lozano-Ondoua 2013)

Lozano-Ondoua AN, Hanlon KE, Symons-Liguori AM, Largent-Milnes TM, Havelin JJ, Ferland HL, 3rd, Chandramouli A, Owusu-Ankomah M, Nikolich-Zugich T, Bloom AP, Jimenez-Andrade JM, King T, Porreca F, Nelson MA, Mantyh PW, Vanderah TW. Disease modification of breast cancer-induced bone remodeling by cannabinoid 2 receptor agonists. J Bone Miner Res. 2013;28(1):92–107. [PubMed]

LEUKEMIA

Leukemia is a type of bone marrow and blood cancer in which unrestrained proliferation of white blood cells occur, usually accompanied by anemia, impaired blood clotting, and enlargement of the lymph nodes, liver and spleen.

STUDY: Leukemia. In the current study, the effect of THC on the upstream and downstream events that modulate the extracellular signal-regulated kinase (ERK) module of mitogen-activated protein kinase pathways primarily in human Jurkat leukemia T cells was investigated. The data suggests that THC-induced apoptosis in Jurkat leukemia T cells occurred and may be regulated by translocation of Bad to mitochondria. (Jia 2006)

Jia W., Hegde VL., Singh NP., et al. Delta9-tetrahydrocannabinol-induced apoptosis in Jurkat leukemia T cells is regulated by translocation of Bad to mitochondria. Mol Cancer Res. 2006;4:549–562. [PubMed]

STUDY: Leukemia. Exposure of leukemia cells to CBD led to CB2-mediated reduction in cell viability and induction in apoptosis (although CBD is considered not to bind to either CB1 or CB2 receptors). It is noteworthy that CBD exposure led to an increase in reactive oxygen species (ROS) production as well as an increase in the expression of the NAD(P)H oxidases Nox4 and p22(phox). (McKallip 2006)

McKallip RJ., Jia W., Schlomer J., Warren JW., Nagarkatti PS., Nagarkatti M. Cannabidiol-induced apoptosis in human leukemia cells: A novel role of cannabidiol in

the regulation of p22phox and Nox4 expression. Mol Pharmacol. 2006;70:897–908. [PubMed]

GLIOMA

Glioma is a tumor originating in the neuroglia of the brain or spinal cord. A glioblastoma is a fast-growing malignant brain tumor of the central nervous system, usually occurring in the cerebrum of adults. Gliomas are a primary group of malignant brain tumors and one of the most aggressive forms of cancer. They exhibit high resistance to conventional chemotherapies. In glioblastoma endothelial cells, CB1 and CB2 receptors were present in about 38% and 54% of the cells respectively, when analyzed by immunohistochemistry. CB2 expression levels were higher in glioblastoma tissues in comparison to CB1. Selective CB2 agonists (activators) may become important targets for the treatment of glioma. Cannabinoids, inhibit tumor growth in animal models by inducing apoptosis of tumor cells and impairing tumor angiogenesis.

PILOT CLINICAL TRIAL: Glioblastoma. THC was administered intratumorally in an initial trial of nine patients with recurrent glioblastoma multiforme, that had previously failed standard therapy (surgery and radiotherapy) and had clear evidence of tumor progression. THC inhibited tumor-cell proliferation in vitro, decreased tumor-cell Ki67 immunostaining and prolonged the survival time of two of the patients. (Guzman 2006)

Guzman M., Duarte MJ., Blazquez C., et al. A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. Br J Cancer. 2006;95:197–203. [PMC free article] [PubMed]

STUDY: Anti-tumor and anti-inflammatory effects on malignant glioma. Cannabinoids suppress the NF-κB inflammatory pathway and cell growth via CB1 receptors in glioma cells provides evidence for the therapeutic potential of targeting cannabinoid receptors for the treatment of inflammation-dependent tumor progression. (Echigo 2012)

Echigo R, Sugimoto N, Yachie A, Ohno-Shosaku T. Cannabinoids inhibit peptidoglycan-induced phosphorylation of NF-κB and cell growth in U87MG human malignant glioma cells. Oncol Rep. 2012 Oct;28(4):1176-80. doi: 10.3892/or.2012.1937. Epub 2012 Jul 26. [PubMed]

STUDY: THC and Glioblastoma. Several experimental approaches were used, which identified delta-9-tetrahydrocannabinol (Delta(9)-THC) as an essential mediator of cannabinoid antitumoral action. In conculsion, Delta(9)-THC was shown to significantly affect viability of glioblastoma multiforme (GBM) cells via a mechanism that appears to elicit G(1) arrest due to down-regulation of E2F1 and Cyclin A. Hence, it is suggested that Delta(9)-THC and other cannabinoids be implemented in future clinical evaluation as a therapeutic modality for brain tumors. (Galanti 2008)

Galanti G, Fisher T, Kventsel I, Shoham J, Gallily R, Mechoulam R, Lavie G, Amariglio N, Rechavi G, Toren A. Delta 9-tetrahydrocannabinol inhibits cell cycle progression by downregulation of E2F1 in human glioblastoma multiforme cells. Acta Oncol. 2008;47(6):1062-70. [PubMed]

STUDY: Malignant gliomas. Glioma stem-like cells constitute one of the potential origins of gliomas. Cannabinoids are known to exert an antitumoral action on gliomas that relies on at least two mechanisms: induction of apoptosis of transformed cells and inhibition of tumor angiogenesis. However, whether cannabinoids target human glioma stem cells and their potential impact in gliomagenesis are unknown. Here, we show that glioma stem-like cells derived from glioblastoma multiforme biopsies and the glioma cell lines U87MG and U373MG express cannabinoid CB1 and CB2 receptors and other elements of the endocannabinoid system. The cannabinoid agonists HU-210 and JWH-133 promoted glial differentiation in a CB receptor-dependent manner. Moreover, cannabinoid challenge decreased the efficiency of glioma stem-like cells to initiate glioma formation in vivo. In gene array experiments, CB receptor activation altered the expression of genes involved in the regulation of stem cell proliferation and differentiation. Results demonstrate that cannabinoids target glioma stem-like cells, promote their differentiation, and inhibit gliomagenesis, thus giving further support to their potential use in the management of malignant gliomas. (Aguado 2007)

Aguado T., Carracedo A., Julien B., et al. Cannabinoids induce glioma stem-like cell differentiation and inhibit gliomagenesis. J Biol Chem. 2007;282:6854–6862. [PubMed]

STUDY: CBD and glioma cells. The nonpsychoactive cannabidiol (CBD) induces apoptosis of glioma cells in vitro and tumor regression in vivo. In another pathway, CBD produced a gradual, time-dependent activation of caspase-3, which preceded the appearance of apoptotic death. In addition, release of cytochrome c and caspase-9 and caspase-8 activation were detected. The exposure to CBD caused in glioma cells an early production of reactive oxygen species (ROS), depletion of intracellular glutathione and increase activity of glutathione reductase and glutathione peroxidase enzymes. Under the same experimental condition, CBD did not impair primary glia.

The present study found a different sensitivity to the anti-proliferative effect of CBD by triggering caspase activation and oxidative stress in human glioma cells. (Massi 2006)

Massi P., Vaccani A., Bianchessi S., Costa B., Macchi P., Parolaro D. The nonpsychoactive cannabidiol triggers caspase activation and oxidative stress in human glioma cells. Cell Mol Life Sci. 2006;63:2057–2066. [PubMed]

STUDIES: Glioma cancer. Δ9-THC and JWH-133 inhibits MMP-2 expression in in vivo model of glioma, leading to apoptosis of tumor cells. The growth inhibitory effect of

these cannabinoids is prevented by blocking ceramide synthesis, and the expression of the stress protein p8. (Blazquez 2003) (Carracedo 2006) (Carracedo 2008)

Blazquez C, Casanova ML, Planas A, Gomez Del Pulgar T, Villanueva C, Fernandez-Acenero MJ, Aragones J, Huffman JW, Jorcano JL, Guzman M. Inhibition of tumor angiogenesis by cannabinoids. Faseb J. 2003;17(3):529–531. [PubMed]

Carracedo A, Lorente M, Egia A, Blazquez C, Garcia S, Giroux V, Malicet C, Villuendas R, Gironella M, Gonzalez-Feria L, Piris MA, Iovanna JL, Guzman M, Velasco G. The stress-regulated protein p8 mediates cannabinoid-induced apoptosis of tumor cells. Cancer Cell. 2006;9(4):301–312. [PubMed]

Blazquez C, Salazar M, Carracedo A, Lorente M, Egia A, Gonzalez-Feria L, Haro A, Velasco G, Guzman M. Cannabinoids inhibit glioma cell invasion by down-regulating matrix metalloproteinase-2 expression. Cancer Res. 2008;68(6):1945–1952. [PubMed]

STUDY: Glioma cell death. Both Δ9-THC and WIN-55,212-2 resulted in sustained activation of ERK1/2 and inhibition of AKT, leading to proapoptic activity. Authors suggest that the increase of proapoptotic Bad activity is an important link between the inhibition of survival pathways and an onset of execution phase of cannabinoid-induced glioma cell death. (Ellert-Miklaszewska 2005)

Ellert-Miklaszewska A, Kaminska B, Konarska L. Cannabinoids down-regulate PI3K/Akt and Erk signalling pathways and activate proapoptotic function of Bad protein. Cell Signal. 2005;17(1):25–37. [PubMed]

STUDY: Glioma antitumor action. Δ9-THC induced eukaryotic translation initiation factor 2alpha (eIF2alpha) phosphorylation and thereby activated an ER stress response that promoted autophagy via tribbles homolog 3-dependent (TRB3-dependent) inhibition of the Akt/mammalian target of rapamycin complex 1 (mTORC1) axis [105]. The activation of this pathway was necessary for the antitumor action of cannabinoids in vivo. (Salazar 2009)

Salazar M, Carracedo A, Salanueva IJ, Hernandez-Tiedra S, Lorente M, Egia A, Vazquez P, Blazquez C, Torres S, Garcia S, Nowak J, Fimia GM, Piacentini M, Cecconi F, Pandolfi PP, Gonzalez-Feria L, et al. Cannabinoid action induces autophagy-mediated cell death through stimulation of ER stress in human glioma cells. J Clin Invest. 2009;119(5):1359–1372. [PMC free article] [PubMed]

STUDY: Glioma cell apoptosis with CBD. CBD treatment induces apoptosis in glioma cells in vitro and tumor regression in vivo through activation of caspases and reactive oxygen species via receptor-independent manner. Furthermore, studies revealed that CBD induced TRPV2-dependent Ca2+ influx which triggers the drug uptake and synergizes with cytotoxic agents to induce apoptosis of glioma cells. (Nabissi 2013)

Nabissi M, Morelli MB, Santoni M, Santoni G. Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents. Carcinogenesis. 2013;34(1):48–57. [PubMed]

STUDY: Glioblastoma growth inhibition. Authors thought that CBD which do not specifically interact with CB1/CB2 receptors, can modulate the activity of Δ9-THC. On that basis Marcu et al determined the growth inhibitory effect of CBD in combination with Δ9-THC in the U251 and SF126 glioblastoma cell lines. (Marcu 2010)

Marcu JP, Christian RT, Lau D, Zielinski AJ, Horowitz MP, Lee J, Pakdel A, Allison J, Limbad C, Moore DH, Yount GL, Desprez PY, McAllister SD. Cannabidiol enhances the inhibitory effects of delta9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival. Mol Cancer Ther. 2010;9(1):180–189. [PMC free article] [PubMed]

STUDY: Glioma antitumoral action. The combined treatment of Δ9-THC and temozolomide (TMZ) exert a strong antitumoral action in glioma xenografts by inducing autophagy [108]. The submaximal doses of Δ9-THC and CBD in combination with TMZ produced a strong antitumoral action in both TMZ-sensitive and TMZ-resistant tumors. (Torres 2011)

Torres S, Lorente M, Rodriguez-Fornes F, Hernandez-Tiedra S, Salazar M, Garcia-Taboada E, Barcia J, Guzman M, Velasco G. A combined preclinical therapy of cannabinoids and temozolomide against glioma. Mol Cancer Ther. 2011;10(1):90–103. [PubMed]

STUDY: Glioma tumor reduction. Treatment of KM-233 (novel cannabinoid ligand) caused a time dependent change in the phosphorylation profiles of MEK, ERK1/2, Akt, BAD, STAT3, and p70S6K in U87MG human GBM cells. At 12mg/kg daily dose of KM-233 for 20 days revealed around 80% reduction in tumor size in the orthotopic model of U87MG. (Gurley 2012)

Gurley SN, Abidi AH, Allison P, Guan P, Duntsch C, Robertson JH, Kosanke SD, Keir ST, Bigner DD, Elberger AJ, Moore BM., 2nd Mechanism of anti-glioma activity and in vivo efficacy of the cannabinoid ligand KM-233. J Neurooncol. 2012;110(2):163–177. [PubMed]

STUDIES: Overcoming glioma cell therapy resistance. Glioma cells develop resistance to cannabinoid treatment due to the upregulation of Amphiregulin (EGFR family ligand) and the growth factor midkine (Mdk). Amphiregulin expression was associated with increased ERK activation and Mdk mediated its protective effect through ALK which interferes with autophagic glioma cell death.

The silencing of amphiregulin and Mdk or ALK pharmacological inhibition can overcome drug resistance of glioma to cannabinoids antitumoral action. Furthermore, to

improve the efficacy of cannabinoids action, microencapsulation methods were used which facilitates a sustained release of the two cannabinoids for several days. Administration of CBD- and THC-loaded poly-ε-caprolactone microparticles reduced tumor growth, cell proliferation and increased apoptosis in mice bearing glioma xenografts with the same efficacy as a daily local administration of these drugs in solution. (Lorente 2009) (Lorente 2011) (Lorente 2011) (Perez de la Ossa 2013)

Lorente M, Carracedo A, Torres S, Natali F, Egia A, Hernandez-Tiedra S, Salazar M, Blazquez C, Guzman M, Velasco G. Amphiregulin is a factor for resistance of glioma cells to cannabinoid-induced apoptosis. Glia. 2009;57(13):1374–1385. [PubMed]

Lorente M, Torres S, Salazar M, Carracedo A, Hernandez-Tiedra S, Rodriguez-Fornes F, Garcia-Taboada E, Melendez B, Mollejo M, Campos-Martin Y, Lakatosh SA, Barcia J, Guzman M, Velasco G. Stimulation of the midkine/ALK axis renders glioma cells resistant to cannabinoid antitumoral action. Cell Death Differ. 2011;18(6):959–973. [PMC free article] [PubMed]

Lorente M, Torres S, Salazar M, Carracedo A, Hernandez-Tiedra S, Rodriguez-Fornes F, Garcia-Taboada E, Melendez B, Mollejo M, Campos-Martin Y, Barcia JA, Guzman M, Velasco G. Stimulation of ALK by the growth factor midkine renders glioma cells resistant to autophagy-mediated cell death. Autophagy. 2011;7(9):1071–1073. [PubMed]

Hernan Perez de la Ossa D, Lorente M, Gil-Alegre ME, Torres S, Garcia-Taboada E, Aberturas Mdel R, Molpeceres J, Velasco G, Torres-Suarez AI. Local delivery of cannabinoid-loaded microparticles inhibits tumor growth in a murine xenograft model of glioblastoma multiforme. PLoS One. 2013;8(1):e54795. [PMC free article] [PubMed]

LYMPHOMA

Lymphoma refers to any lymphoid tissue malignancy.

STUDY: Lymphoma and leukemia cell apoptosis. CB1 and CB2 receptors were over-expressed in mantle cell lymphoma (MCL), and B cell non-Hodgkin lymphoma. Δ9-THC inhibits cell viability and increased apoptosis both in vitro in EL4 and MCL cells and EL4 tumor bearing mice. In next studies the combination of Δ9-THC and other cytotoxic agents induced apoptosis in leukemia cells by MAPK/ERK pathway. (Flygare 2005) (Wasik 2011) (Liu 2008)

Flygare J, Gustafsson K, Kimby E, Christensson B, Sander B. Cannabinoid receptor ligands mediate growth inhibition and cell death in mantle cell lymphoma. FEBS Lett. 2005;579(30):6885–6889. [PubMed]

Wasik AM, Christensson B, Sander B. The role of cannabinoid receptors and the endocannabinoid system in mantle cell lymphoma and other non-Hodgkin lymphomas. Semin Cancer Biol. 2011;21(5):313–321. [PubMed]

Liu WM, Scott KA, Shamash J, Joel S, Powles TB. Enhancing the in vitro cytotoxic activity of Delta9-tetrahydrocannabinol in leukemic cells through a combinatorial approach. Leuk Lymphoma. 2008;49(9):1800–1809. [PubMed]

STUDY: Mantle cell lymphoma (MCL) cytotoxicity. R(+)-methanandamide and WIN-55,212-2 induced apoptosis in MCL cells, was associated with ceramide accumulation and p38, depolarization of the mitochondrial membrane, and caspase activation. (Gustafsson 2009)

Gustafsson K, Sander B, Bielawski J, Hannun YA, Flygare J. Potentiation of cannabinoid-induced cytotoxicity in mantle cell lymphoma through modulation of ceramide metabolism. Mol Cancer Res. 2009;7(7):1086–1098. [PMC free article] [PubMed]

STUDY: Mantle cell lymphoma (MCL) apoptosis induced. R(+)-methanandamide induced apoptosis in MCL cells. (Gustafsson 2006)

Gustafsson K, Christensson B, Sander B, Flygare J. Cannabinoid receptor-mediated apoptosis induced by R(+)-methanandamide and Win55,212-2 is associated with ceramide accumulation and p38 activation in mantle cell lymphoma. Mol Pharmacol. 2006;70(5):1612–1620. [PubMed]

STUDY: Apoptosis-resistant Mantle cell lymphoma (MCL). Cannabinoids decreased cell viability as assessed by metabolic activity. The persistent expression of mammalian homolog of Atg8 with microtubule-associated protein-1 light chain-3 II (LC3 II) and p62, as well as the lack of protection from chloroquine, indicates that lysosomal degradation is not involved in this cytoplasmic vacuolation process, distinguishing from classical autophagy. Paraptosis-like cell death, a third type of a programmed cell death occurred in response to cannabinoids. (Wasik 2011)

Wasik AM, Almestrand S, Wang X, Hultenby K, Dackland AL, Andersson P, Kimby E, Christensson B, Sander B. WIN55,212-2 induces cytoplasmic vacuolation in apoptosis-resistant MCL cells. Cell Death Dis. 2011;2:e225. [PMC free article] [PubMed]

ORAL CANCER

Oral cancer mainly occurs in the mouth, including the lips, tongue and throat. Smoking, tobacco chewing and alcohol consumption increases the incidence of oral cancer. Radiation therapy and surgery are the common treatments for oral cancer.

STUDY: Oral squamous cell carcinoma (OSCC). Δ9-THC induced apoptosis in oral squamous cell carcinoma (OSCC), a malignant form of oral cancer. (Lopes 2012)

Lopes CF, de Angelis BB, Prudente HM, de Souza BV, Cardoso SV, de Azambuja Ribeiro RI. Concomitant consumption of marijuana, alcohol and tobacco in oral squamous cell carcinoma development and progression: recent advances and challenges. Arch Oral Biol. 2012;57(8):1026–1033. [PubMed]

HEAD AND NECK CANCER

Marijuana smoking increases the incidence of head and neck cancer in young people but its constituent, cannabinoids have anti-tumor properties.

STUDY: Head and neck squamous cell carcinoma (HNSCC). One study reports that moderate marijuana use is associated with reduced risk of HNSCC. Notable observations: Among marijuana users moderate weekly use was associated with reduced risk; 10 to 20 years of marijuana use was associated with a significantly reduced risk of HNSCC; and the magnitude of reduced risk was more pronounced for those who started use at an older age. (Liang 2009)

Liang C, McClean MD, Marsit C, Christensen B, Peters E, Nelson HH, Kelsey KT. A population-based case-control study of marijuana use and head and neck squamous cell carcinoma. Cancer Prev Res (Phila) 2009;2(8):759–768. [PMC free article] [PubMed]

THYROID CARCINOMA - Thyroid cancer occurs when cells of the thyroid gland become abnormal, grow uncontrollably and form a tumor mass.

STUDY: Thyroid carcinoma. Tumorigenicity of anaplastic thyroid carcinoma cell line ARO was significantly reduced following interleukin (IL)-12 gene transfer. A considerable regression of thyroid tumors generated by inoculation of ARO/CB2 cells was observed in nude mice following local administration of JWH133. Study data suggests that CB2 overexpression may contribute to the regression of human anaplastic thyroid tumor in nude mice following IL-12 gene transfer. Given that cannabinoids have shown antitumor effects in many types of cancer models, CB2 may be a viable therapeutic target for the treatment of anaplastic thyroid carcinoma. (Shi 2008)

Shi Y, Zou M, Baitei EY, Alzahrani AS, Parhar RS, Al-Makhalafi Z, Al-Mohanna FA. Cannabinoid 2 receptor induction by IL-12 and its potential as a therapeutic target for the treatment of anaplastic thyroid carcinoma. Cancer Gene Ther. 2008;15(2):101–107. [PubMed]

STUDY: Thyroid carcinoma. The CB2 agonist JWH-133 and CB1/CB2 agonist WIN-55,212-2 induced apoptosis in ARO and ARO/IL-12 cells. 2-methyl-2'-F-anandamide (Met-F-AEA) also induced apoptosis in thyroid carcinoma cells via activation of p53 and p21 mediated pathway. (Cozzolino 2010)

Cozzolino R, Cali G, Bifulco M, Laccetti P. A metabolically stable analogue of anandamide, Met-F-AEA, inhibits human thyroid carcinoma cell lines by activation of apoptosis. Invest New Drugs. 2010;28(2):115–123. [PubMed]

OTHER CONDITIONS

PSORIASIS

STUDY: Inhibits PSORIASIS. Psoriasis is an inflammatory disease also characterised in part by epidermal keratinocyte hyper-proliferation. In this study the cannabinoids tested all inhibited keratinocyte proliferation in a concentration-dependent manner. The selective CB2 receptor agonists JWH015 and BML190 elicited only partial inhibition, the non-selective CB agonist HU210 produced a concentration-dependent response. Results show that cannabinoids inhibit human keratinocyte proliferation, and therefore support a potential role for cannabinoids in the treatment of psoriasis. (Wilkinson 2007)

Wilkinson JD, Williamson EM. Cannabinoids inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and have a potential therapeutic value in the treatment of psoriasis.J Dermatol Sci. 2007 Feb;45(2):87-92. Epub 2006 Dec 6. [PubMed]

GASTROINTESTINAL (GI) DISORDERS

PHYSIOLOGY REVIEW: GASTROINTESTINAL (GI) tract and cannabinoids. In the GI tract, cannabinoid type 1 (CB1) receptors are present in neurons of the enteric (intestinal) nervous system and in sensory terminals of vagal and spinal neurons. Activation of CB1 receptors was shown to modulate several functions in the GI tract, including gastric secretion, gastric emptying and intestinal motility. Under pathophysiological conditions induced experimentally in rodents, the endocannabinoid system conveys protection to the GI tract (e.g. from inflammation and abnormally high gastric and enteric secretions). Thus, the endocannabinoid system may serve as a potentially promising therapeutic against different GI disorders, including inflammatory bowel diseases (e.g. Crohn's disease), functional bowel diseases (e.g. irritable bowel syndrome) and secretion- and motility-related disorders. As stimulation of this modulatory system by CB1 receptor agonists can lead to unwanted psychotropic side effects, an alternative and promising avenue for therapeutic applications resides in the

treatment with CB1 receptor agonists that are unable to cross the blood-brain barrier, or with compounds that inhibit the degradation of endogenous ligands (endocannabinoids) of CB1 receptors, hence prolonging the activity of the endocannabinoid system. (Massa 2005)

Massa F, Storr M, Lutz B. The endocannabinoid system in the physiology and pathophysiology of the gastrointestinal tract. J Mol Med (Berl). 2005 Dec;83(12):944-54. Epub 2005 Aug 26. [PubMed]

OBSERVATIONAL STUDY: Gastrointestinal pain. THC given to a Mediterranean fever patient with chronic relapsing pain and gastrointestinal inflammation showed a highly significant reduction in pain. (Holdcroft 1997)

Holdcroft A., Smith M., Jacklin A., et al. Pain relief with oral cannabinoids in familial Mediterranean fever. Anaesthesia. 1997;52:483–486. [PubMed]

NIGHT VISION IMPROVEMENT

STUDY: Night vision improvement. Field-testing of night vision was accomplished in two settings. One study examines the results of double-blinded graduated THC administration 0-20 mg (as Marinol) versus placebo in one subject on measures of dark adaptometry and scotopic sensitivity. Analogous field studies were performed in Morocco with the SST-1 in three subjects before and after smoking kif (cannabis herb). In both test situations, improvements in night vision measures were noted after THC or cannabis. It is believed that this effect is dose-dependent and cannabinoid-mediated at the retinal level. (Russo 2004)

Russo EB, Merzouki A, Mesa JM, Frey KA, Bach PJ. Cannabis improves night vision: a case study of dark adaptometry and scotopic sensitivity in kif smokers of the Rif mountains of northern Morocco.J Ethnopharmacol. 2004 Jul;93(1):99-104. [PubMed]

GENITO-URINARY TRACT IRRITATION – according to folklore traditions, cannabis has been used effectively for this.

ANTIBIOTIC for gram-positive BACTERIA; MALARIA

OTHER – General Effects of Cannabis Use

STUDY: THC and CBD can have opposite effects. A study conducted on healthy volunteers revealed that Delta-9-tetrahydrocannabinol and Cannabidiol (CBD) can have opposite effects on regional brain function, which may underlie their different

symptomatic and behavioral effects, and CBD's ability to block the psychotogenic effects of Delta-9-THC. (Bhattacharyya 2010)

Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, Nosarti C, O' Carroll CM, Seal M, Allen P, Mehta MA, Stone JM, Tunstall N, Giampietro V, Kapur S, Murray RM, Zuardi AW, Crippa JA, Atakan Z, McGuire PK. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. 2010 Feb;35(3):764-74. doi: 10.1038/npp.2009.184. Epub 2009 Nov 18. [PubMed]

STUDY REVIEW: THC and CBD increases clinical efficacy. The hypothesis that the combination of THC and CBD increases clinical efficacy while reducing adverse events is supported. (Russo 2006)

Russo E., Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses. 2006;66:234–246. [PubMed]

STUDY REVIEW: CBD Antipsychotic effects. In the review, both preclinical and clinical studies investigating the potential antipsychotic effects of both cannabidiol and SR141716 are presented together with the possible underlying mechanisms of action. (Roser 2010)

Roser P, Vollenweider FX, Kawohl W. Potential antipsychotic properties of central cannabinoid (CB1) receptor antagonists. World J Biol Psychiatry. 2010 Mar;11(2 Pt 2):208-19. doi: 10.3109/15622970801908047. [PubMed]

REVIEW: CBD Effects. Cannabidiol, the main non-psychotropic component of the glandular hairs of Cannabis sativa displays a plethora of actions including anticonvulsive, sedative, hypnotic, antipsychotic, antiinflammatory and neuroprotective properties. (Scuderi 2008)

Scuderi C, Filippis DD, Iuvone T, Blasio A, Steardo A, Esposito G. Cannabidiol in medicine: a review of its therapeutic potential in CNS disorders. Phytother Res. 2009 May;23(5):597-602. doi: 10.1002/ptr.2625. [PubMed]

STUDY: Increased Pupil Size. Results about effect of a smoked kif preparation (Cannabis sativa L.) on pupil diameter variations after 30 mn in 34 eyes of 17 volunteer-consumers in a dark closed room were presented. Results reveal a significant increase in pupil size post kif. (Merzouki 2008)

Merzouki A, Molero Mesa J, Louktibi A, Kadiri M, Urbano GV. Assessing changes in pupillary size in Rifian smokers of kif (Cannabis sativa L.). J Forensic Leg Med. 2008 Jul;15(5):335-8. doi: 10.1016/j.jflm.2007.08.001. Epub 2007 Nov 26. [PubMed]

OTHER - Safety

STUDY: THS vaporization safe. The study carried out to investigate vaporization using the Volcano(R) device as an alternative means of delivery of inhaled Cannabis sativa in eighteen healthy inpatient subjects shows vaporization of cannabis is a safe and effective mode of delivery of tetrahydrocannabinol. (Abrams 2007)

Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. Clin Pharmacol Ther. 2007 Nov;82(5):572-8. Epub 2007 Apr 11. [PubMed]

APPENDIX

CANNABINOIDS

Source: Chakravarti B, Ravi J, Ganju RK. Cannabinoids as therapeutic agents in cancer: current status and future implications. Onco 2014 Aug 15;5(15):5852-72. [PubMed] [Free PMC Article]

CANNABINOIDS are divided into 3 main categories:

1- PHYTOCANNABINOIDS (Plant-derived)

- Δ9- tetrahydrocannabinol (THC), also known as Delta-9 THC, or even just THC; CB1/CB2 receptor agonist
  -Analgesic, antiemetic, appetite stimulant tumor growth inhibitor.
- Δ8-tetrahydrocannabinol (Δ8-THC) also known as Delta-8 THC; CB1/CB2 agonist
  -Anti-tumor agent, inhibitors of mitochondrial O2 consumption in human sperm, antiemetic, appetite stimulant
- Cannabidiol (CBD); CB1 agonist
  -Anti-tumor agent, attenuate catalepsy (muscular rigidity and decreased sensitivity to pain), immunosuppressive, inflammatory or anti-inflammatory agent (depends upon used concentration of drug), antipsychotics (moderates THC)
- Cannabinol (CBN)
- Cannabigerol (CBG)
  -Multiple sclerosis, antiemetic, anti-inflammatory agent, treatment for neurological disorder
- Cannabichromene (CBC)
  -anti-inflammatory agent, treatment for neurological disorder, hypomotility, antinociception, catalepsy, and hypothermia
- Cannabicyclol (CBL)
- Cannabivarin (CBV)
- Tetrahydrocannabivarin (THCV)
  -Hepatic ischaemia, anti-inflammatory
- Cannabidivarin (CBDV)
- Cannabichromevarin (CBCV)
- Cannabigerovarin (CBGV)
  -Anti-inflammatory
- Cannabigerol Monoethyl Ether (CBGM)

2- ENDOCANNABINOIDS (Found inside the body)

- N-arachidonoylethanolamine (AEA-anandamide); CB1 agonist (activator)
  -Analgesic, antiemetic, appetite stimulant, tumor growth inhibitor
- Arachidonoylglycerol (2-AG); CB1/CB2 agonist
  -Analgesic, antiemetic, appetite stimulant, tumor growth inhibitor
- Palmitoyl-ethanolamide (PEA), or N-(2-Hydroxyethyl) hexadecamide (N-acyl-ethanolamide); CB2 agonist
  -Neuromodulatory and immunomodulatory
- Docosatetraenylethanolamide; CB1 agonist
  -Neuromodulatory and immunomodulatory
- Homo-γ-linoenylethanolamide; CB1 agonist
  -Neuromodulatory and immunomodulatory
- Oleamide, or cis-9-octadecenoamide; CB1 agonist
  -Neuromodulatory and immunomodulatory

3- SYNTHETIC CANNABINOIDS

- HU-210; CB1/ CB2 Nonselective agonist (activator)
  -Analgesic, multiple sclerosis, neuroprotective
- CP-55,940; CB1/ CB2 Nonselective agonist
  -Anti-cancer agent, Analgesic, antiemetic, appetite stimulant.
- R-(+)-WIN 55,212-2; CB1/ CB2 Nonselective agonist
  -Analgesic, Antiemetic, appetite stimulant, tumor growth inhibitor, multiple sclerosis
- JWH-015; CB2 selective agonist
  -Anti-tumor, anti-inflammatory, antiemetic
- JWH-133; CB2 selective agonist
  -Neurological disorders, Anti-cancer
- JWH-139; CB2 selective agonist
  -Analgesic, antiemetic, appetite stimulant tumor growth inhibitor
- HU-308; CB2 selective agonist
  -Tumor growth inhibitor (in glioma, skin carcinoma, lymphoma
- CP55940; CB1/CB2 agonist
  -Analgesic, antiemetic, appetite stimulant, tumor growth inhibitor, multiple sclerosis
- R-(+)-methanandamide; CB1 agonist
  -Analgesic, antiemetic, appetite stimulant tumor growth inhibitor
- AM251; CB1 antagonist (blocker)
  -Metabolic syndrome
- AM281; CB1 antagonist (blocker)
  -Improves recognition loss induced by naloxone in morphine withdrawal mice, various pharmacological property