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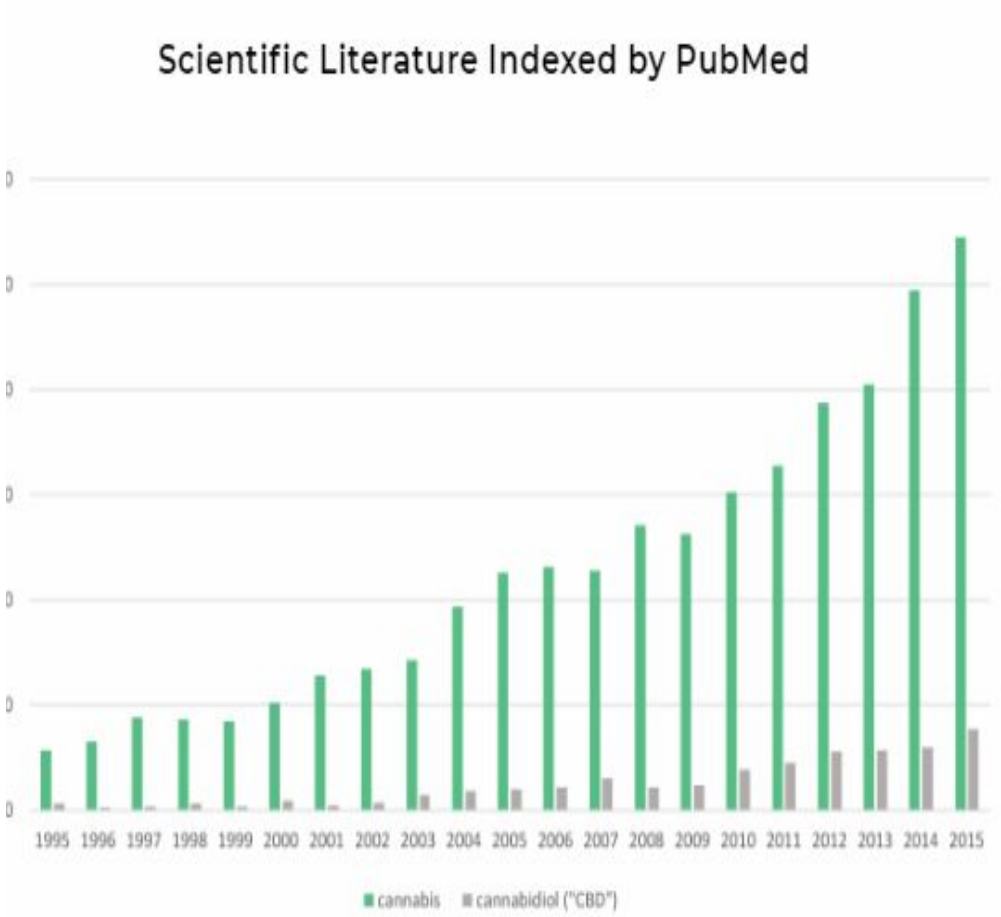
An Overview of Cannabidiol (CBD) and Current Evidence of Therapeutic Application

Presentation Outline

- Brief history of Cannabidiol (CBD)
- Cannabinoids
- Endocannabinoid System
- The Cannabinoid Entourage Effect
- Current and Emerging Evidence of Therapeutic Applications
- CBD Bioavailability, Tolerability and Toxicity

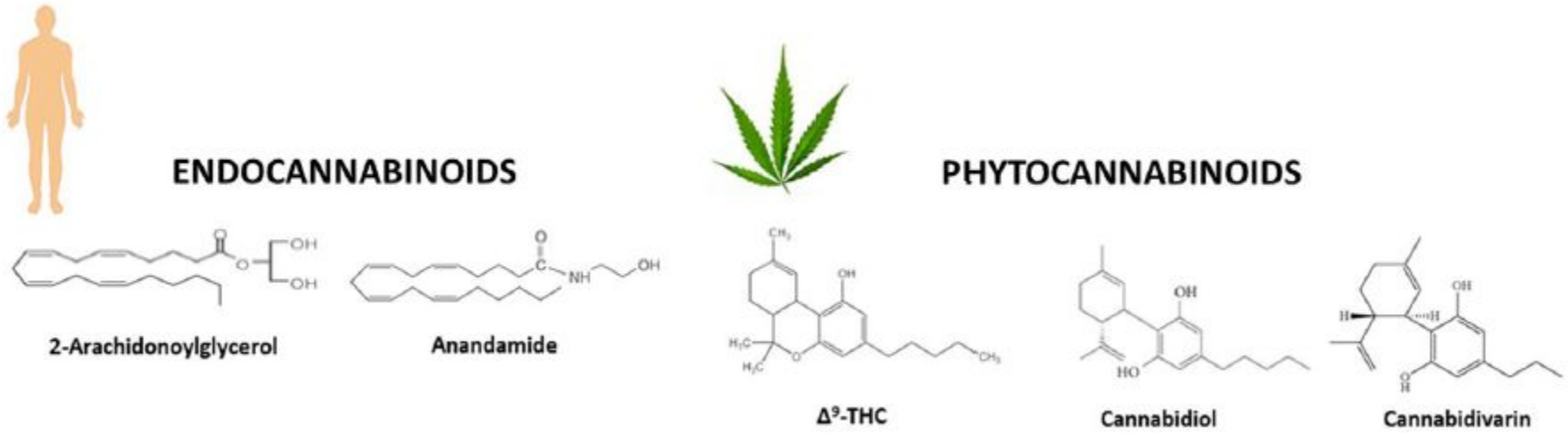
Brief History of Cannabidiol

- Cannabis has been cultivated for its medicinal, psychoactive, and physical properties for thousands of years
- The earliest recorded medicinal uses of the plant date as far back as 1400-2000 BC
- In the 19th century, William Osler, M.D., considered to be a “Father of Modern Medicine”, was a proponent of the medicinal use of cannabis
- CBD was first discovered by Dr. Roger Adams and his team at the University of Illinois in 1940 but it’s chemical structure wasn’t elucidated until 1963
- Dr. Raphael Mechoulam, considered the ‘Father of Cannabis Research’, is recognized for this, as well as the isolation of THC and discovery of the brain’s endogenous cannabinoid
- While CBD was discovered more than 20 years earlier, THC has dominated cannabis research until recently



Cannabinoids

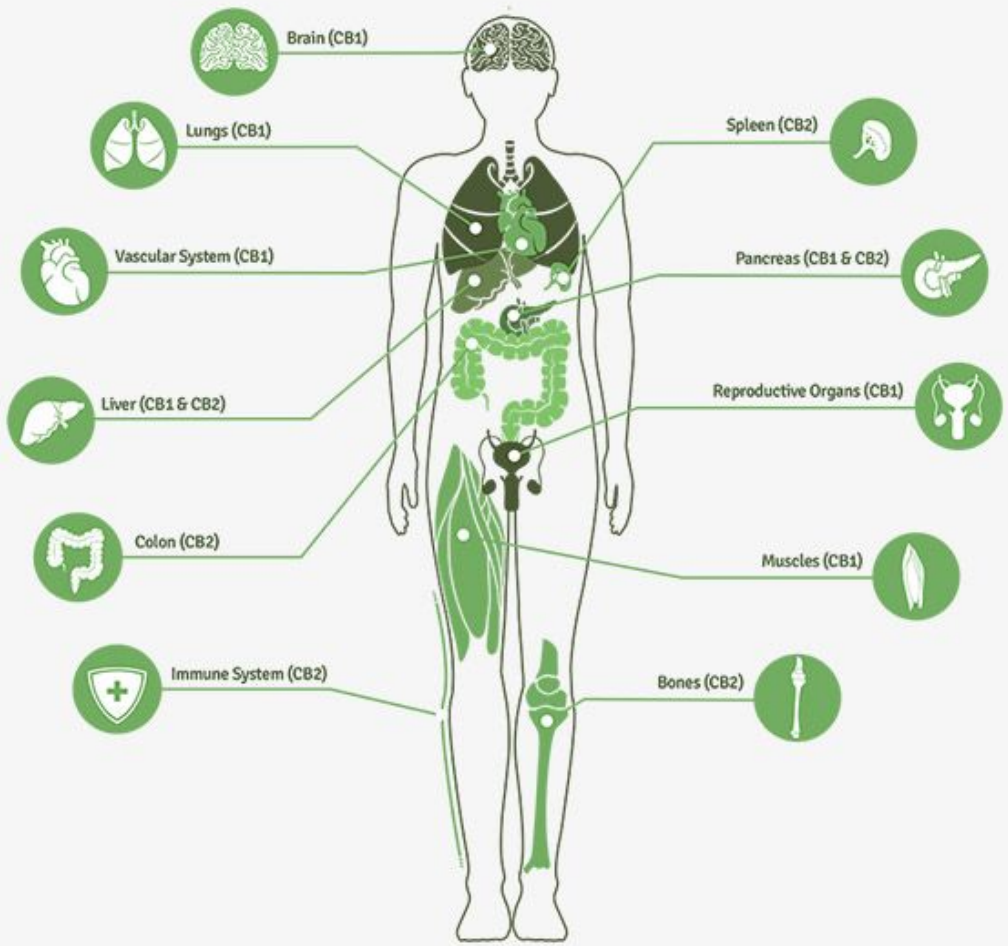
- There are 2 primary, endogenous endocannabinoids: anandamide (AEA), taken from the Sanskrit word *ananda*, which means "joy, bliss" and 2-arachidonyl glycerol (2-AG)
- Cannabinoids exert their activity via a specific system of cellular receptors widely distributed throughout the body referred to as the endocannabinoid system
- THC and CBD, are the most abundant of the > 80 active exogenous cannabinoids within the cannabis plant, collectively referred to as phytocannabinoids
- Phytocannabinoid pharmacology is still not completely understood, but there appears to be a balancing effect between THC and CBD



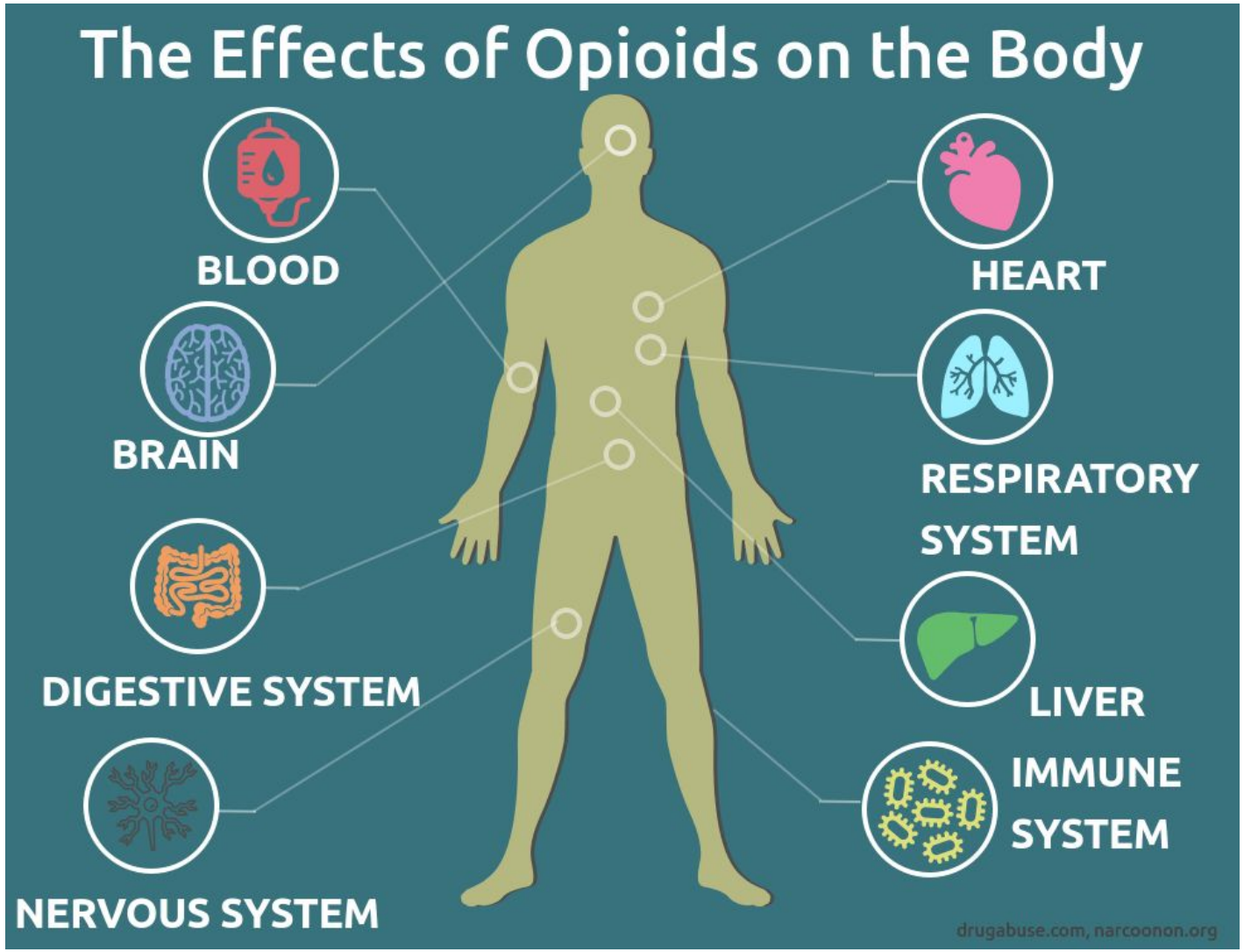
Endocannabinoid System

- The endocannabinoid system (ECS) is now recognized as a major signaling system not only in the brain but in peripheral tissues as well
- It has been called one of the most widespread and versatile signaling systems ever discovered
- The ECS is thought to regulate numerous physiologic processes, including pain, mood, memory, learning, addiction, and appetite
- The ECS is influenced by both endocannabinoids and phytocannabinoids

THE BODY'S ENDOCANNABINOID SYSTEM



The Body's Opioid System



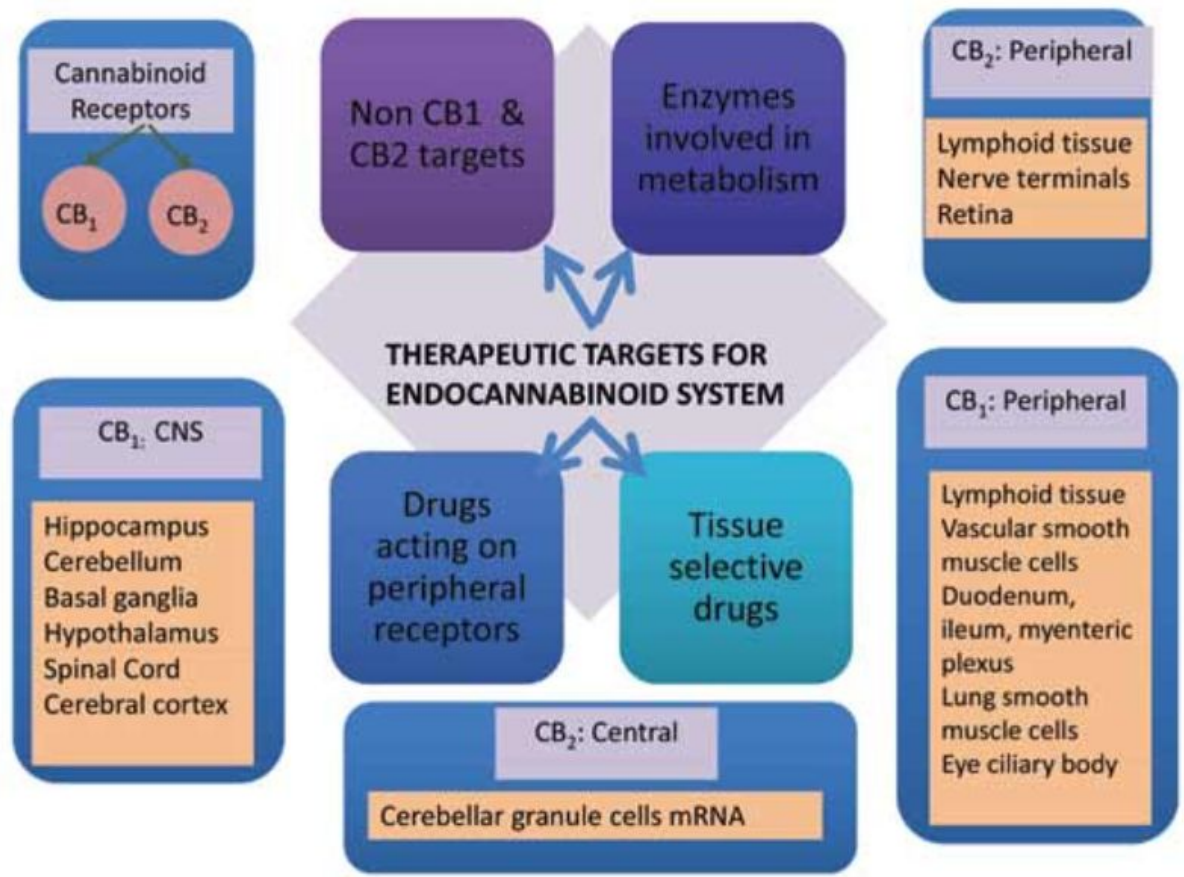
Review Article

Endocannabinoid System: A Multi-Facet Therapeutic Target

Author(s): Rimplejeet Kaur, Sneha R. Ambwani, Surjit Singh.

Journal Name: Current Clinical Pharmacology

Volume 11 , Issue 2 , 2016 **DOI** : 10.2174/1574884711666160418105339



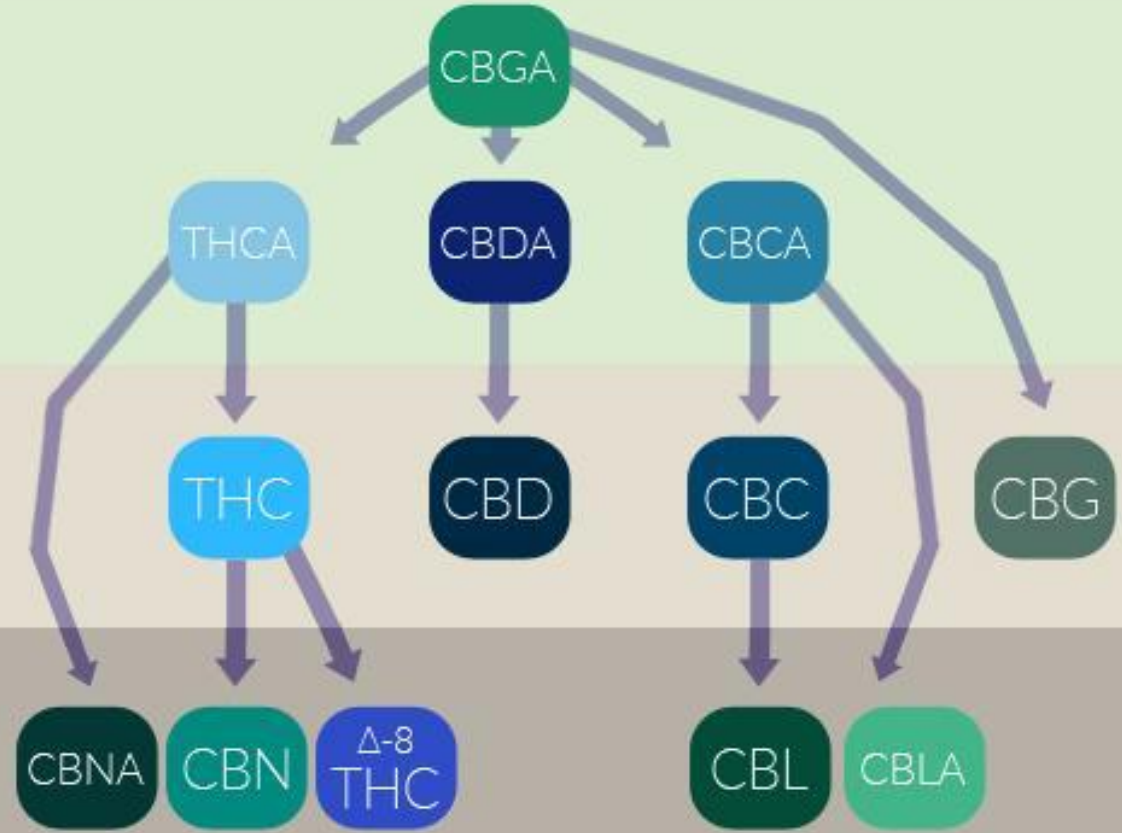
UNDERSTANDING THE RELATIONSHIP BETWEEN CANNABINOIDS

RAW
Fresh, uncured cannabis remains in its acidic form

Conversion begins immediately after harvest

DRIED / HEATED
Decarboxylation occurs, converting from an acid to the active compound

AGED
Created over time after exposure to oxygen, heat, and UV light



Health Effects of Marijuana	THC	THC-A	THC-V	CBN	CBD	CBD-A	CBC	CBC-A	CBG	CBG-A	Benefits
Pain relief	■			■	■		■		■		Analgesis
Reduces inflammation		■			■	■	■		■	■	Anti-inflamatory
Supresses appetite			■								Anoretic
Stimulates appetite	■				■						Appetite stimulant
Reduces vomiting and nausea	■				■						Antimetic
Reduces contractions of small intestine					■						Intestinal antiprokinetic
Relieves anxiety					■						Anxiolytic
Tranquilizing / psychosis management					■						Antipsychotic
Reduces seizures and convulsions		■	■		■						Antiepileptic
Suppresses muscle spasms	■			■	■						Antispasmodic
Aides sleep				■							Anti-insomnia
Reduces efficacy of immune system					■						Immunosuppresive
Reduces blood sugar levels			■		■						Anti-diabetic
Prevents nervous system degeneration					■						Neuroprotective
Treats psoriasis					■						Antipsioratic
Reduces risk of artery blockage					■						Anti-ischemic
Kills or slows bacteria growth					■		■	■	■		Anti-bacterial
Treats fungal infection								■	■		Anti-fungal
Inhibits cell growth in tumours / cancer		■			■	■	■		■		Anti-proliferative
Promotes bone growth			■		■		■		■		Bone-stimulant

J Nephropharmacol. 2015; 4(1): 27–30.
Published online 2015 Jan 1.
PMCID: PMC5297475
PMID: 28197471

Herbal versus synthetic drugs; beliefs and facts

Ali Karimi, [1] Maedeh Majlesi, [2] and Mahmoud Rafieian-Kopaei [1,*]

- There are some “drug like” plant remedies whose actions approach that of pharmaceuticals
- The herbal medicines contain a lot of different compounds, some of them demonstrating great complexities. It has been shown that the whole plants extracts cannot be mimicked by administering purified and isolated constituents of the herbs
- The sciences believe that the whole plant is greater than the sum of the parts which reflects the inherent conservatism of the medical establishment
- In this regard, a pharmaceutical drug is usually designed to elicit a specific reaction and its “side or adverse effects” are usually traded as a “risk” against the “benefit” of the primary effect
- Herbal medicines usually tend to have several broad complementary or synergistic actions on physiological systems at the same time which are usually in the same general therapeutic direction, and often non-specific. Furthermore, these actions are rarely adverse effects

Entourage (Synergistic) Effect in Cannabis

BJP British Journal of Pharmacology

Themed Issue: Cannabinoids in Biology and Medicine, Part I

REVIEW

Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects

Ethan B Russo

GW Pharmaceuticals, Salisbury, Wiltshire, UK

DOI:10.1111/j.1476-5381.2011.01238.x
www.brjpharmacol.org

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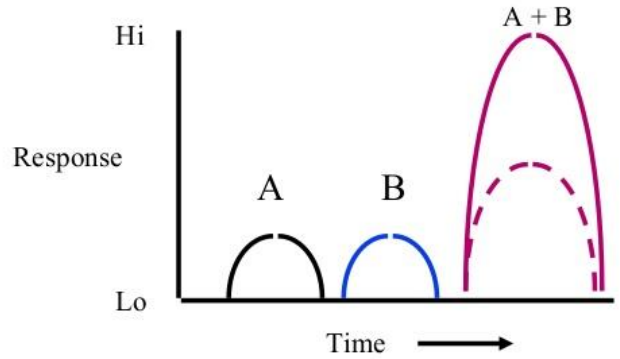
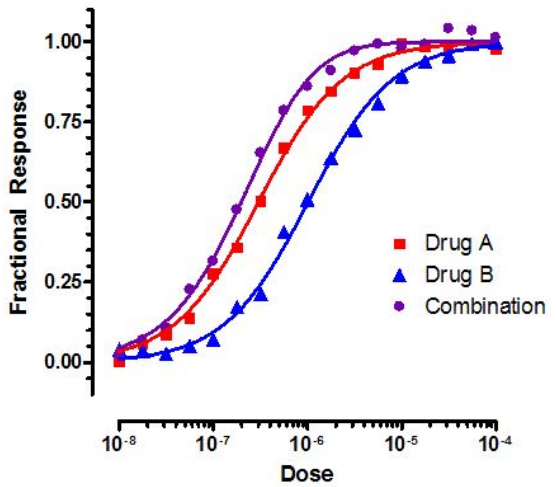
Keywords
cannabinoids; terpenoids; essential oils; THC; CBD; limonene; pinene; linalool; caryophyllene; phytotherapy

Received
19 November 2010
Revised
29 December 2010
Accepted
12 January 2011

Synergistic Effects



The effect of two chemicals taken together is greater than the sum of their separate effect at the same doses, e.g., alcohol and other drugs



Phytocannabinoid-Terpenoid Entourage Effects

- Terpenes are organic, aromatic hydrocarbons that can be found in thousands of plants around the world
- Cannabis contains a large number of terpenes that are therapeutically beneficial to the human body
- Terpenes play an important role in the treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer and bacterial and fungal infections
- Myrcene and limonene are the first and second most prominent terpenes in cannabis respectively

TERPENES	EFFECTS	ALSO FOUND IN	MEDICAL BENEFITS
MYRCENE	Sedating, relaxing, enhances THC's psychoactivity	Mango, thyme, citrus, lemongrass, bay leaves	Antiseptic, anti-bacterial, antifungal, inflamation
CARYOPHYLLENE	No detectable physical effects	Pepper, cloves, hops, basil, oregano	Antioxidant, inflamation, muscle spams, pain, insomnia
LINALOOL	Sedating, calming	Lavander, citrus, laurel, birch, resewood	Insomnia, stress, depression, anxiety, pain, convulsions
PINENE	Memory retention, alerthness	Pine needles, conifer, sage	Inflamation, asthma (bronchodilator)
HUMELENE	Supresses appetite	Hops, coriander	Anti-infilamatory, anty-bacterial, pain
LIMONENE	Elevated mood, stress relief	Citrus rinds, juniper, peppermint	Anti-depression, anti-anxiety, gastric reflux, antifungal

Phytocannabinoid-Terpenoid Entourage Effects

- 4 basic mechanisms of synergy have been proposed (Wagner and Ulrich-Merzenich, 2009)
- Multitarget effects
- Pharmacokinetic effects such as improved solubility or bioavailability
- Agent interactions affecting bacterial resistance
- Modulation of adverse events (adverse side effects)

TERPENES	EFFECTS	ALSO FOUND IN	MEDICAL BENEFITS
MYRCENE	Sedating, relaxing, enhances THC's psychoactivity	Mango, thyme, citrus, lemongrass, bay leaves	Antiseptic, anti-bacterial, antifungal, inflamation
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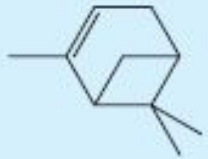
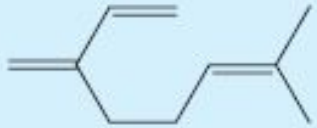
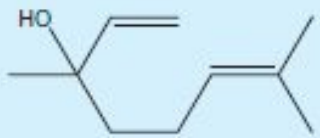
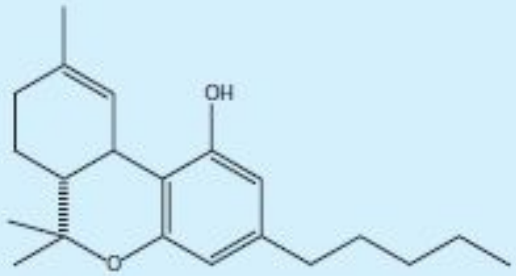
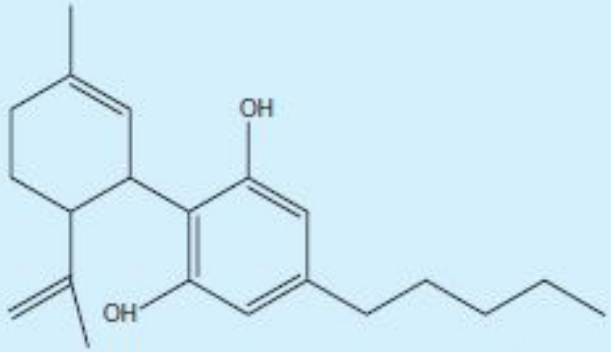
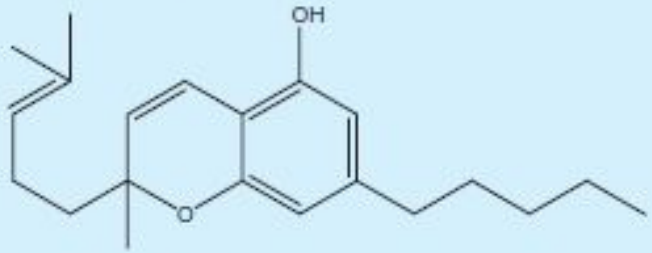
Terpenoid	Structure	Commonly encountered in	Pharmacological activity (Reference)	Synergistic cannabinoid
Limonene		 Lemon	Potent AD/immunostimulant via inhalation (Komori *et al.*, 1995)	CBD
			Anxiolytic (Carvalho-Freitas and Costa, 2002; Pultrini Ade *et al.*, 2006) via 5-HT_{1A} (Komiya *et al.*, 2006)	CBD
			Apoptosis of breast cancer cells (Vigushin *et al.*, 1998)	CBD, CBG
			Active against acne bacteria (Kim *et al.*, 2008)	CBD
			Dermatophytes (Sanguinetti *et al.*, 2007; Singh *et al.*, 2010)	CBG
			Gastro-oesophageal reflux (Harris, 2010)	THC
α-Pinene		 Pine	Anti-inflammatory via PGE-1 (Gil *et al.*, 1989)	CBD
			Bronchodilatory in humans (Falk *et al.*, 1990)	THC
			Acetylcholinesterase inhibitor, aiding memory (Perry *et al.*, 2000)	THC?, CBD
β-Myrcene		 Hops	Blocks inflammation via PGE-2 (Lorenzetti *et al.*, 1991)	CBD
			Analgesic, antagonized by naloxone (Rao *et al.*, 1990)	CBD, THC
			Sedating, muscle relaxant, hypnotic (do Vale *et al.*, 2002)	THC
			Blocks hepatic carcinogenesis by aflatoxin (de Oliveira *et al.*, 1997)	CBD, CBG
Linalool		 Lavender	Anti-anxiety (Russo, 2001)	CBD, CBG?
			Sedative on inhalation in mice (Buchbauer *et al.*, 1993)	THC
			Local anesthetic (Re *et al.*, 2000)	THC
			Analgesic via adenosine A_{2A} (Peana *et al.*, 2006)	CBD
			Anticonvulsant/anti-glutamate (Elisabetsky *et al.*, 1995)	CBD, THCV, CBDV
			Potent anti-leishmanial (do Socorro *et al.*, 2003)	?

Phytocannabinoid structure	Selected pharmacology (reference)	Synergistic terpenoids
 delta-9-tetrahydrocannabinol (THC)	Analgesic via CB_1 and CB_2 (Rahn and Hohmann, 2009)	Various
	AI/antioxidant (Hampson *et al.*, 1998)	Limonene *et al.*
	Bronchodilatory (Williams *et al.*, 1976)	Pinene
	↓ Sx. Alzheimer disease (Volicer *et al.*, 1997; Eubanks *et al.*, 2006)	Limonene, pinene, linalool
	Benefit on duodenal ulcers (Douthwaite, 1947)	Caryophyllene, limonene
	Muscle relaxant (Kavia *et al.*, 2010)	Linalool?
	Antipruritic, cholestatic jaundice (Neff *et al.*, 2002)	Caryophyllene?
 cannabidiol	AI/antioxidant (Hampson *et al.*, 1998)	Limonene *et al.*
	Anti-anxiety via $5\text{-}HT_{1A}$ (Russo *et al.*, 2005)	Linalool, limonene
	Anticonvulsant (Jones *et al.*, 2010)	Linalool
	Cytotoxic versus breast cancer (Ligresti *et al.*, 2006)	Limonene
	↑ adenosine A_{2A} signalling (Carrier *et al.*, 2006)	Linalool
	Effective versus MRSA (Appendino *et al.*, 2008)	Pinene
	Decreases sebum/sebocytes (Biro *et al.*, 2009)	Pinene, limonene, linalool
	Treatment of addiction (see text)	Caryophyllene
 cannabichromene	Anti-inflammatory/analgesic (Davis and Hatoum, 1983)	Various
	Antifungal (ElSohly *et al.*, 1982)	Caryophyllene oxide
	AEA uptake inhibitor (De Petrocellis *et al.*, 2011)	–
	Antidepressant in rodent model (Deyo and Musty, 2003)	Limonene

Current and Emerging Evidence of Therapeutic Applications

- Movement Disorders
- Psychiatric Disorders
- Autoimmune Disorders
- Cancer

Cannabidiol in Movement Disorders

Clinical studies investigating the effects of CBD on movement disorders.

Disease	Main Findings	Duration of Treatment	Dose of CBD and route of administration	Patients characteristics	References
PD	Open-label pilot study. Treatment with CBD for 4 weeks diminished the psychotic symptoms. CBD did not worsen the motor function or induce adverse effects.	4 weeks	150 mg/day of CBD, increasing by 150 mg every week, depending on patients' clinical response. Oral route.	6 PD patients (4 men and 2 women) with psychosis—not controlled with reduction of antiparkinsonian medications—for at least 3 months before the beginning of the study. Patients were in stable doses of anti-PD medication for at least 7 days.	Zuardi et al., 2009
PD	Case series. CBD reduced the frequency of the events related to REM sleep behavior disorder.	6 weeks	75 mg/day (3 patients) or 300 mg/day (1 patient) of CBD. Oral route.	4 PD male patients with REM sleep behavior disorder, with at least two episodes of complex sleep-related behaviors per week.	Chagas et al., 2014a
PD	Exploratory double-blind trial. Treatment with CBD did not improve the motor function or the general symptoms score, but the higher dose (300 mg/kg) improved quality of life.	6 weeks	75 or 300 mg/day of CBD. Oral route.	21 PD patients (15 men and 6 women) in stable doses of anti-PD medication for at least 30 days before the beginning of the study.	Chagas et al., 2014b

Cannabidiol in Movement Disorders

HD	Case report of HD patients treated with cannabinoid. Cannabinoids improved UHDRS motor score and dystonia subscore.	6 or 9 months	Sativex: 12 or 7 sprays/day. Intranasal route.	2 male HD patients with complains of severe dystonia. Duration of the disease: 14 and 16 years.	Saft et al., 2018
Dystonic movement disorders	Open label study. Treatment with CBD resulted on 20–50% improvement of the dystonic symptoms. Two patients with simultaneous PD's signs showed worsening of their hypokinesia and/or resting tremor when receiving the higher doses of CBD (over 300 mg/day).	6 weeks	Increasing doses of CBD from 100 to 600 mg/day. Oral route.	5 patients (4 men and 1 woman) with dystonic movements, 2 with simultaneous parkinsonian symptoms.	Consroe et al., 1986
Dystonic movement disorders	Case report. CBD improved the dystonic symptoms without inducing adverse effects.	One administration	CBD 200 mg. Oral route.	2 patients: one woman with idiopathic spasmodic torticollis and one man with generalized torsion dystonia.	Sandyk et al., 1986

Front Pharmacol. 2018; 9: 482.
Published online 2018 May 11. doi: 10.3389/fphar.2018.00482
PMCID: PMC5958190
PMID: 29867488

Cannabidiol as a Promising Strategy to Treat and Prevent Movement Disorders?

Fernanda F. Peres,[1,2,*†] Alvaro C. Lima,[1,†] Jaime E. C. Hallak,[2,3] José A. Crippa,[2,3] Regina H. Silva,[1] and Vanessa C. Abílio[1,2]

Cannabidiol in Psychiatric Disorders

J Psychopharmacol. 2011 Jan;25(1):121-30. doi: 10.1177/0269881110379283. Epub 2010 Sep 9.

Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report.

Crippa JA[1], Derenusson GN, Ferrari TB, Wichert-Ana L, Duran FL, Martin-Santos R, Simões MV, Bhattacharyya S, Fusar-Poli P, Atakan Z, Santos Filho A, Freitas-Ferrari MC, McGuire PK, Zuardi AW, Busatto GF, Hallak JE.

The aim of the present study was to investigate this in patients with generalized social anxiety disorder (SAD) using functional neuroimaging. Relative to placebo, CBD was associated with significantly decreased subjective anxiety ($p < 0.001$)

Neuropsychopharmacology. 2011 May;36(6):1219-26. doi: 10.1038/npp.2011.6. Epub 2011 Feb 9.

Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients.

Bergamaschi MM[1], Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, Quevedo J, Roesler R, Schröder N, Nardi AE, Martín-Santos R, Hallak JE, Zuardi AW, Crippa JA.

This preliminary study aimed to compare the effects of a simulation public speaking test (SPST) on healthy control (HC) patients and treatment-naïve SAD patients who received a single dose of CBD or placebo

Pretreatment with CBD significantly reduced anxiety, cognitive impairment and discomfort in their speech performance, and significantly decreased alert in their anticipatory speech. The placebo group presented higher anxiety, cognitive impairment, discomfort, and alert levels when compared with the control group

Cannabidiol in Psychiatric Disorders

Transl Psychiatry. 2012 Mar 20;2:e94. doi: 10.1038/tp.2012.15.

Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia.

Leweke FM[1], Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, Klosterkötter J, Hellmich M, Koethe D.

A double-blind, randomized clinical trial of cannabidiol vs amisulpride, a potent antipsychotic, in acute schizophrenia. Both treatment were safe and led to significant clinical improvement, but cannabidiol displayed a markedly superior side-effect profile. Moreover, cannabidiol treatment was accompanied by a significant increase in serum anandamide levels, which was significantly associated with clinical improvement.

Addict Behav. 2013 Sep;38(9):2433-6. doi: 10.1016/j.addbeh.2013.03.011. Epub 2013 Apr 1.

Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings.

Morgan CJ[1], Das RK, Joye A, Curran HV, Kamboj SK.

24 smokers were randomised to receive an inhaler of CBD (n=12) or placebo (n=12) for one week, they were instructed to use the inhaler when they felt the urge to smoke. Over the treatment week, placebo treated smokers showed no differences in number of cigarettes smoked.
In contrast, those treated with CBD significantly reduced the number of cigarettes smoked by ~40% during treatment.

Cannabidiol in Psychiatric Disorders

Epilepsy Behav. 2018 Nov;88:162-171. doi: 10.1016/j.yebeh.2018.07.027. Epub 2018 Oct 2.

Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: A randomized, double-blind, controlled trial.

Schoedel KA[1], Szeto I[2], Setnik B[3], Sellers EM[4], Levy-Cooperman N[5], Mills C[6], Etges T[7], Sommerville K[8].

Administration of a therapeutic dose of CBD (750 mg) showed significantly low abuse potential in a highly sensitive population of polydrug users

J Autism Dev Disord. 2018 Oct 31. doi: 10.1007/s10803-018-3808-2. [Epub ahead of print]

Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems-A Retrospective Feasibility Study.

Aran A[1], Cassuto H[2], Lubotzky A[3], Wattad N[3], Hazan E[3].

This retrospective study assessed tolerability and efficacy of cannabidiol-rich cannabis, in 60 children with ASD and severe behavioral problems. Following the cannabis treatment, behavioral outbreaks were much improved or very much improved in 61% of patients

Cannabidiol in Autoimmune Disorders

J Neurol Neurosurg Psychiatry. 2012 Nov;83(11):1125-32. doi: 10.1136/jnnp-2012-302468. Epub 2012 Jul 12.

Multiple sclerosis and extract of cannabis: results of the MUSEC trial.

Zajicek JP[1], Hobart JC, Slade A, Barnes D, Mattison PG; MUSEC Research Group.

Objectives: To determine the efficacy and safety of a standardized extract of Cannabis sativa given orally 2 times daily as compared to placebo for the relief of muscle stiffness and pain in multiple sclerosis for a period of 12 weeks in 400 multiple sclerosis patients from 20 neurological clinics in the United Kingdom.

Results: The rate of relief from muscle stiffness after 12 weeks was almost twice as high with oral cannabis extract than with placebo (29.4% vs. 15.7%; OR 2.26; 95% CI 1.24 to 4.13; p=0.004, one sided). Similar results were found after 4 weeks and 8 weeks, and also for all further CRSs. Results from the MS scales supported these findings.

Conclusions: The study met its primary objective to demonstrate the superiority of CE over placebo in the treatment of muscle stiffness in MS. No new safety concerns were observed.

Cannabidiol in Autoimmune Disorders

Inflamm Bowel Dis. 2018 Mar 19;24(4):680-697. doi: 10.1093/ibd/izy014.

The Use of Cannabinoids in Colitis: A Systematic Review and Meta-Analysis.

Couch DG[1], Maudslay H[1], Doleman B[1], Lund JN[1], O'Sullivan SE[1].

Results: From 2008 papers, 51 publications examining the effect of cannabinoid compounds on murine colitis and 2 clinical studies were identified. Cannabidiol, a phytocannabinoid, was the most investigated drug.

Conclusions: There is abundant preclinical literature demonstrating the anti-inflammatory effects of cannabinoid drugs in inflammation of the gut. Larger randomized controlled-trials are warranted.

Cannabidiol in Cancer

Anticancer Res. 2018 Oct;38(10):5831-5835. doi: 10.21873/anticanres.12924.

Report of Objective Clinical Responses of Cancer Patients to Pharmaceutical-grade Synthetic Cannabidiol.

Table I. *Tabular presentation of our results on 119 cancer patients.*

Cancer type	Tumour free	Stable disease	Extended median survival	Slowed progression	No effect/ result	Died	CBD as only treatment	Unknown outcome	Total cases
Anaplastic ependymoma			3				3		3
DIPG			1				1		1
Glioblastoma multiforme			4	3		3	4		7
Bladder		1	1						2
Breast	7	21	8		3	6	6		39
Head and Neck	1			1					2
Prostate		10	3			3	6		16
Neuroendocrine		1							1
Non-Hodgkin's lymphoma	1	6				1	3		8
Non-small cell lung			2			2	2		2
Colorectal	1		9	2	1	6			13
Pancreatic			2			2	2		4
Ovarian			5	1		3	1		6
Miscellaneous	2	6	5	1	1	1		1	15
Total	12	45	43	8	5	27	28	1	119

Clinical responses were seen in 92% of the 119 cases with solid tumors including a reduction in circulating tumor cells in many cases and in other cases, a reduction in tumor size, as shown by repeat scans. No side-effects of any kind were observed when using pharmaceutical grade synthetic cannabidiol.

Case Study

Experimental study patient is 50 year old female suffering from pain and mobility related symptoms of multiple autoimmune disorders (Systemic Lupus Erythematosus, Raynaud's disease and Rheumatoid Arthritis). She has been managed by conventional medical therapeutics for many years, achieving only intermittent alleviation of her pain, inflammation and swelling of multiple joints. Moreover, prolonged use of certain conventional therapies (steroids, NSAIDs) have resulted in significant side effects that now prevent her from safely tolerating their ongoing use.

On medical interview, subjective complaints included pain and swelling of the hands, lower back, hips, right knee and feet, with exacerbations of lower back and hip pain so intense causing inability to sit or even walk, with missed work days. Physical examination indicated decreased range of motion in the cervical, thoracic and lumbar spinal columns; decreased range of motion and strength in shoulders bilaterally and decreased strength of the right lower limb. Significant swelling was not present but for the exception of bilateral pedal edema. Laboratory evaluation revealed significantly elevated levels of the inflammatory biomarkers C-Reactive Protein and ESR Westergren.

Case Study

Methods: The patient was started on a 28 day regimen of highly purified (99.9%) cannabidiol (CBD) isolate. The CBD was administered sublingually at a dose of 200 mg three times daily. Internationally validated pain and quality of life assessment tools (McGill Pain Questionnaire and SF-36) were completed by the patient immediately prior to treatment and on the final day of treatment. Laboratory evaluation was repeated on the final day of treatment.

Results: Significant improvement of pain and mobility related symptoms was reported within 72 hours of treatment, reaching a maximum therapeutic effect by day 10. Symptoms related to mood (decreased anxiety, increased sense of well-being) continued to improved up to day 21. Pre-treatment McGill Pain score was 52/78. Post-treatment, score (after 4 weeks) decreased to 25/78. Pre-treatment versus post treatment SF-36 scores demonstrated considerable improvement across all 9 health domains.

Pre-treatment C-Reactive Protein and ESR Westergren laboratory values were 4.4 mg/dL and 48 mg/dL. Post-treatment (after 28 days) C-Reactive Protein and ESR Westergren laboratory values were 2.2 mg/dL and 39 mg/dL. Adverse effects of treatment were mild and non-serious, limited to esophageal and stomach irritation post swallowing the CBD tincture.

Conclusion: A highly purified (99.9%) cannabidiol isolate tincture of 600 mg daily dosage regimen was well tolerated and highly effective in decreasing system inflammation while improving quality of life and pain scores on highly validated assessment tools.

- **Oral Administration:** When you swallow a CBD tablet, it is not absorbed directly into the bloodstream. It takes a minute or two to dissolve in the stomach and then be absorbed. Your liver will not metabolize it 100% due to the *first pass effect*. Thus, ingesting CBD has relatively low bioavailability, typically less than 10%. It could also be a while before you feel the benefits of the oral CBD dose. Perhaps as long as an hour.
- **Sublingual Application:** A couple of drops of CBD oil under the tongue takes advantage of mucus membranes in the mouth for increased bioavailability. Assuming the CBD oil is held under the tongue for 60–90 seconds and not accidentally swallowed, the first pass effect is generally avoided. Effects are still not instantaneous and usually take about 20 minutes.
- **Inhalation by Smoking:** Puffing on a CBD-rich cannabis roll up increases CBD bioavailability up to approximately 15–20%. This has become a common consumption method. Effects are usually experienced within minutes due to the way the lungs absorb CBD.
- **Inhalation by Vaping:** Vaporizing CBD takes you into 40–60% high bioavailability territory. Potentially 'healthier' and 3–4 times higher bioavailability than a roll-up, this may be the preferable inhalation route and focus of future medical application using 99% crystalline CBD isolate based liquid carrier solutions.

Tolerability and Toxicology

CNS Drugs. 2018 Nov;32(11):1053-1067. doi: 10.1007/s40263-018-0578-5.

A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects.

Taylor L[1], Gidal B[2], Blakey G[3], Tayo B[1], Morrison G[4].

Methods: The study consisted of three arms: single ascending dose (1500, 3000, 4500 or 6000 mg CBD [n = 6 per group]/placebo [n = 8; 2 per CBD dose group]), multiple dose (750 or 1500 mg CBD [n = 9 per group]/placebo [n = 6; 3 per CBD dose group] twice daily.

Results: CBD was generally well tolerated. Diarrhea, nausea, headache, and somnolence were the most common adverse events (AEs) across all trial arms. All AEs were of mild or moderate severity; none were severe or serious. There were no deaths or discontinuations in the trial. After single oral doses, CBD appeared rapidly in plasma; time to maximum plasma concentration (t_{max}) was approximately 4-5 h

Conclusions: CBD was generally well tolerated. Most AEs were mild in severity; none were severe or serious. The safety and PK profile support twice-daily administration of CBD.

Summary Points of Interest

- Physiological and pharmacological understanding of the endocannabinoid system is limited
- Therapeutic applications involving endogenous and exogenous cannabinoids are only at initial stages of considerable potential
- Cannabidiol demonstrates limited if any toxicity even at extremely high doses, its bioavailability is route dependent, and its therapeutic dosing range remains to be elucidated and standardized

Got Questions?

Pre-treatment

Results RAND 36-Item Health Survey v1.0

Scores represent the percentage of total possible score achieved. (Total possible score is 100%)

Physical functioning: **15%**

Role limitations due to physical health: **0%**

Role limitations due to emotional problems: **0%**

Energy/fatigue: **0%**

Emotional well-being: **36%**

Social functioning: **0%**

Pain: **23%**

General health: **15%**

Health change: **0%**

Post-Treatment

Results RAND 36-Item Health Survey v1.0

Scores represent the percentage of total possible score achieved. (Total possible score is 100%)

Physical functioning: **50%**

Role limitations due to physical health: **75%**

Role limitations due to emotional problems: **67%**

Energy/fatigue: **70%**

Emotional well-being: **76%**

Social functioning: **88%**

Pain: **90%**

General health: **15%**

Health change: **100%**