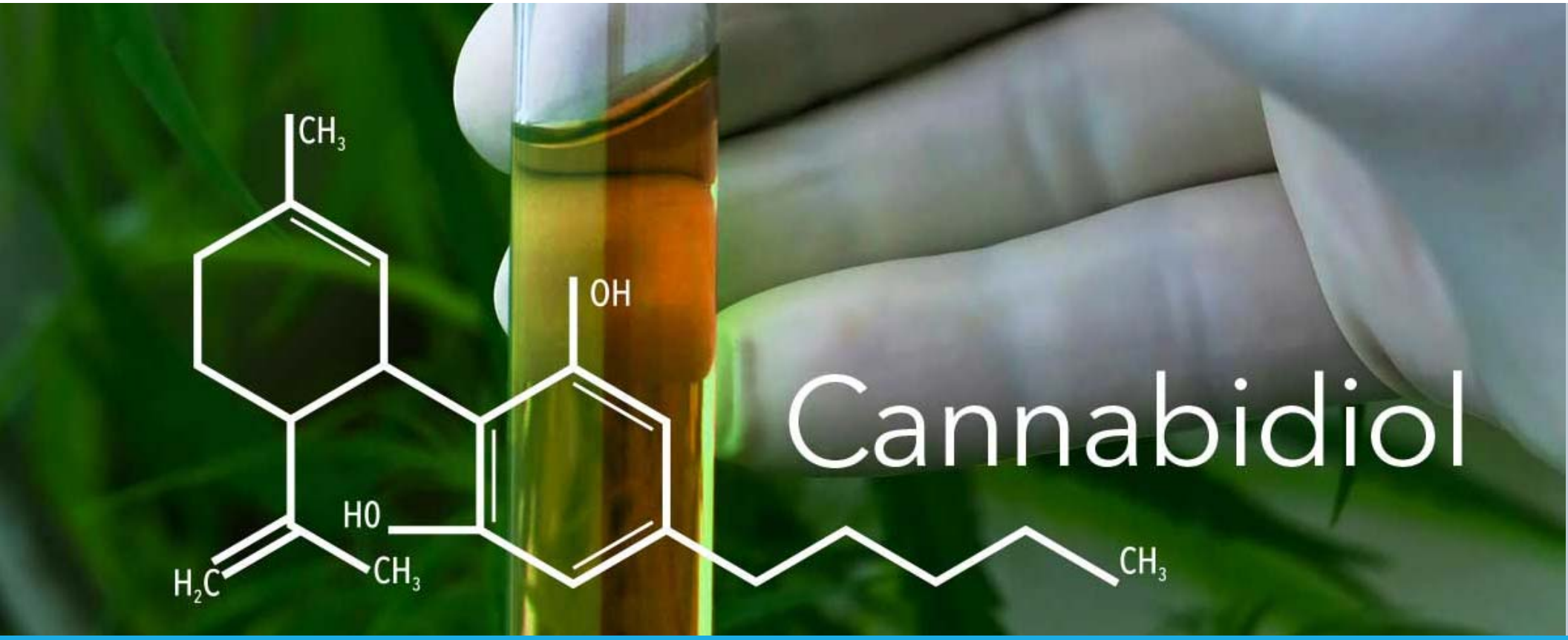


Cannabidiol

What will be discussed

- Overview and History
- Mechanism of Action
- Safety
- PK data
- Effectiveness and Clinical Studies

Overview

- **Cannabidiol**, also known as CBD, is a **non-psychoactive constituent** of **Cannabis sativa**, also known as marijuana.
- Over 80 constituents, known as **cannabinoids**, have been identified from the Cannabis sativa plant, of which **delta-9-tetrahydrocannabinol (THC)** is the major **psychoactive compound**.
- Cannabidiol makes up around **40% of cannabis extracts** and has been investigated for a wide variety of therapeutic effects

Picture from Natural Medicine Database

Overview

- A study published in February 2015 in the **Pharmacology & Pharmacy journal** showed that a **CBD-rich** **extract from cannabis plants is much more efficient than CBD used in its pure form**, mainly due the presence of other cannabinoids, terpenes and other molecules that greatly increase the dosage/efficiency ratio of CBD. That's why using products with all these **other molecules** is so important, so we can have better results than when using exclusively pure CBD.

CBD crystals , 98% purity

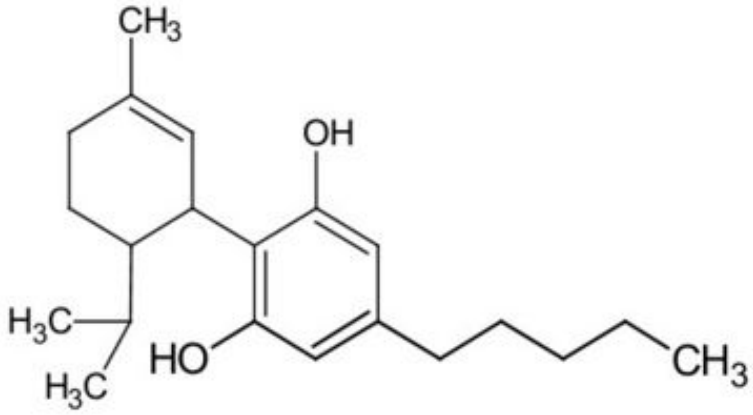
Overview

- Normally, **CBD products** can be purchased as **CBD oils, capsules or sprays**. The exact CBD dosage still remains undefined by the science and greatly varies depending on the disease to treat; most treatments start with a dose of **1mg CBD per Kg of bodyweight** which is gradually increased if necessary.
- An important point to highlight is the **study recently published on the Cannabis and Cannabinoid Research** website (June 2016) which shows that **orally taken CBD may turn into THC** due to the action of the digestive juices in the stomach. That could explain why kids using CBD to treat epilepsy may experience some of the side effects of THC, like sleepiness. Thus, using **CBD sublingually** (under the tongue) is recommended so it does not reach the digestive system.

History

- Cannabidiol was first extracted and isolated from Cannabis sativa in the 1930s.
- In 1963, its chemical structure was elucidated.
- In the 1970s, researchers began to evaluate the pharmacological properties of cannabidiol
- As a **new drug**, cannabidiol products are **not defined as dietary supplements** according to the US Food and Drug Administration (FDA).
- **However**, dietary supplements containing cannabidiol still exist in the marketplace.

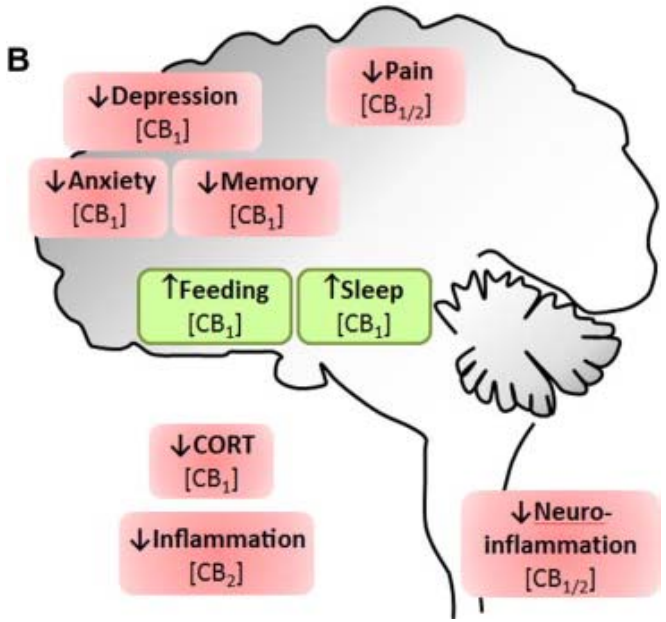
Scientific Name:
2-[(1R,6R)-3-Methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol.



Picture from
http://www.sielc.com/Compound-Cannabidiol.html

Mechanism of Action

- **CB1** is an endocannabinoid receptor primarily located in the **central nervous system** (but not in the medulla) and act primary to **inhibit** the release of neurotransmitters.
- **CB2** is largely found in the **periphery on immune and nerve cells**.
- Functions of the endocannabinoid system in humans: effects on short term memory, neurogenesis, appetite stimulation, analgesia, inhibition of immune function, and reduction of the HPA axis during stress.



Mechanism of Action (cont.)

- **THC** is the primary **psychoactive** cannabinoid in cannabis. It binds with relatively equal affinity to CB1 and CB2; however, most of its effects are associated with **CB1** in the brain.
- The **mode of action of cannabidiol is not fully understood** and **several mechanisms** have been proposed
- **Cannabidiol (CBD)** is another cannabinoid that is **not psychoactive** and **does NOT bind to CB receptors**, but appears to have **anticonvulsant** and **anti-inflammatory** effects. It may also have **antipsychotic effects** (indirect antagonist of CB agonists), **analgesic and antidepressant** effects (mediated via 5HT1a agonism).

Mechanism of Action (cont.)

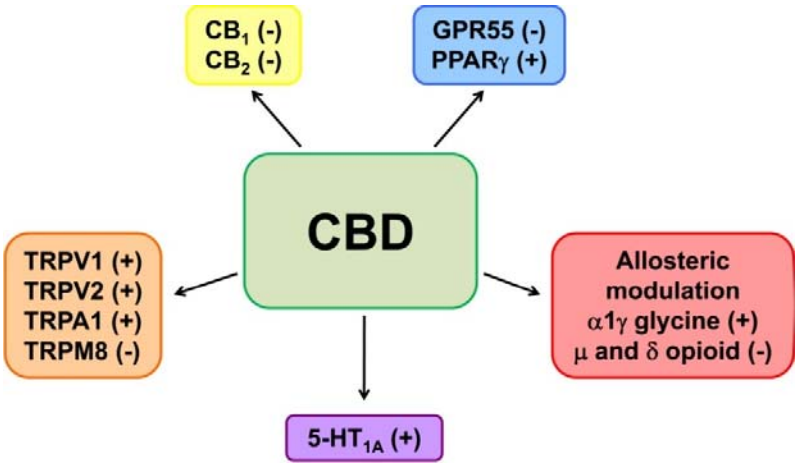
	Serotonin 5HT1A	Vanilloid TRVP-1	Adenosine 2A2	GPR55	FAAH inhibition	antioxidant
Agonist	★	★	★			
Antagonist				★		
Receptor-Independent					★	★
Regulates	depression sleep appetite	pain inflammation body temperature	cardio-vascular other neuro-transmitters	bone density blood pressure cancer cell proliferation	ECB tone	Neuro-protection

CANNABIDIOL'S MECHANISM OF ACTION: a summary of what scientists have learned.

CBD How it works from Martin A Lee (O'Shaughnessy's • Autumn 2011)

Mechanism of Action (cont.)

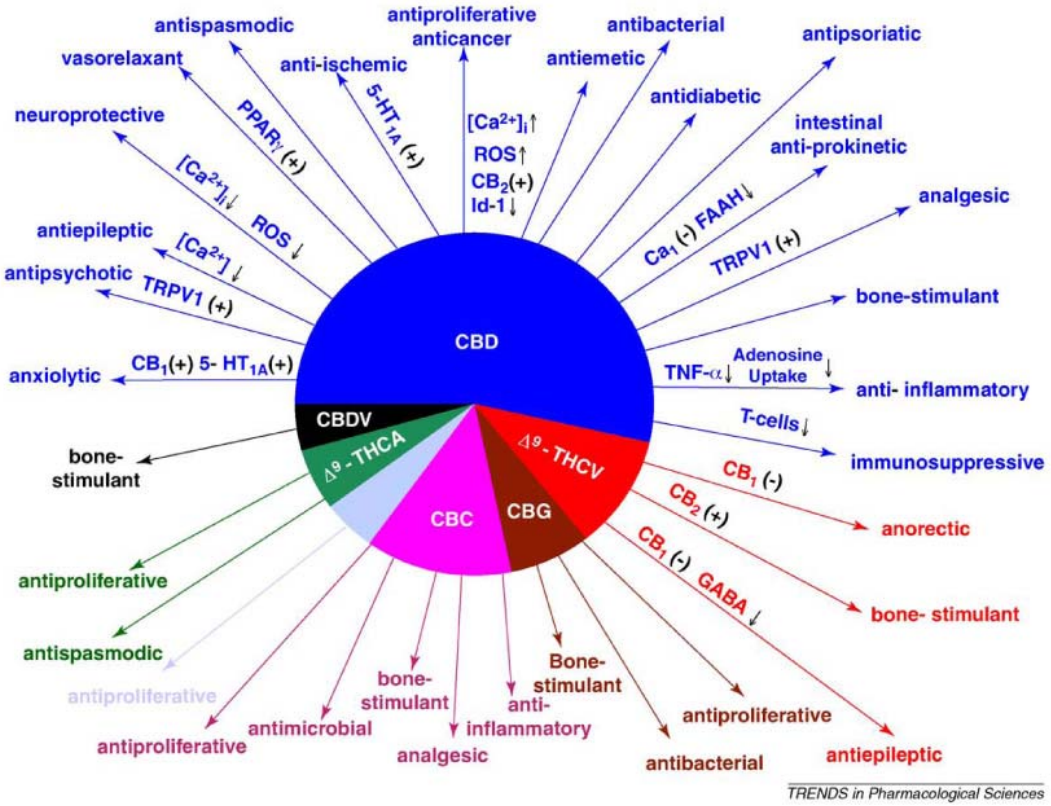
- At **low concentrations**, CBD has been shown to **block** the orphan G-protein-coupled receptor **GPR55,** transient receptor potential of melastatin type 8 **(TRPM8)** channel, and equilibrative nucleoside transporter **(ENT),** as well as **enhance** the activity of the **5-HT_{1A} receptor**, **alpha3 and alpha1 glycine receptors**, and transient receptor potential of ankyrin type 1 **(TRPA1) channel**.
- At **higher concentrations CBD** has been shown to **enhance** the activity of the nuclear peroxisome proliferator-activated receptor-gamma **(PPAR-gamma)** and the transient receptor potential of vanilloid type 1 **(TRPV1)** and 2 **(TRPV2)** channels. CBD also **inhibits** the cellular **uptake** and **degradation** of the **endocannabinoid anandamide**.



Picture from
Cannabidiol and Cancer — An Overview of the Preclinical Data

Mechanism of Action (cont.)

- Unlike delta-9-tetrahydrocannabinol, cannabidiol (CBD) **does not activate** the cannabinoid type 1 **(CB1)** and cannabinoid t 2 **(CB2) receptors** → explain its **lack of psychotropic effects**.
- However, CBD has been shown to interact o interfere with a number of **endocannabinoi** and **non-endocannabinoid signaling system**



Picture from
Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb Review by Cell Press, 2009

Mechanism of Action (cont.)

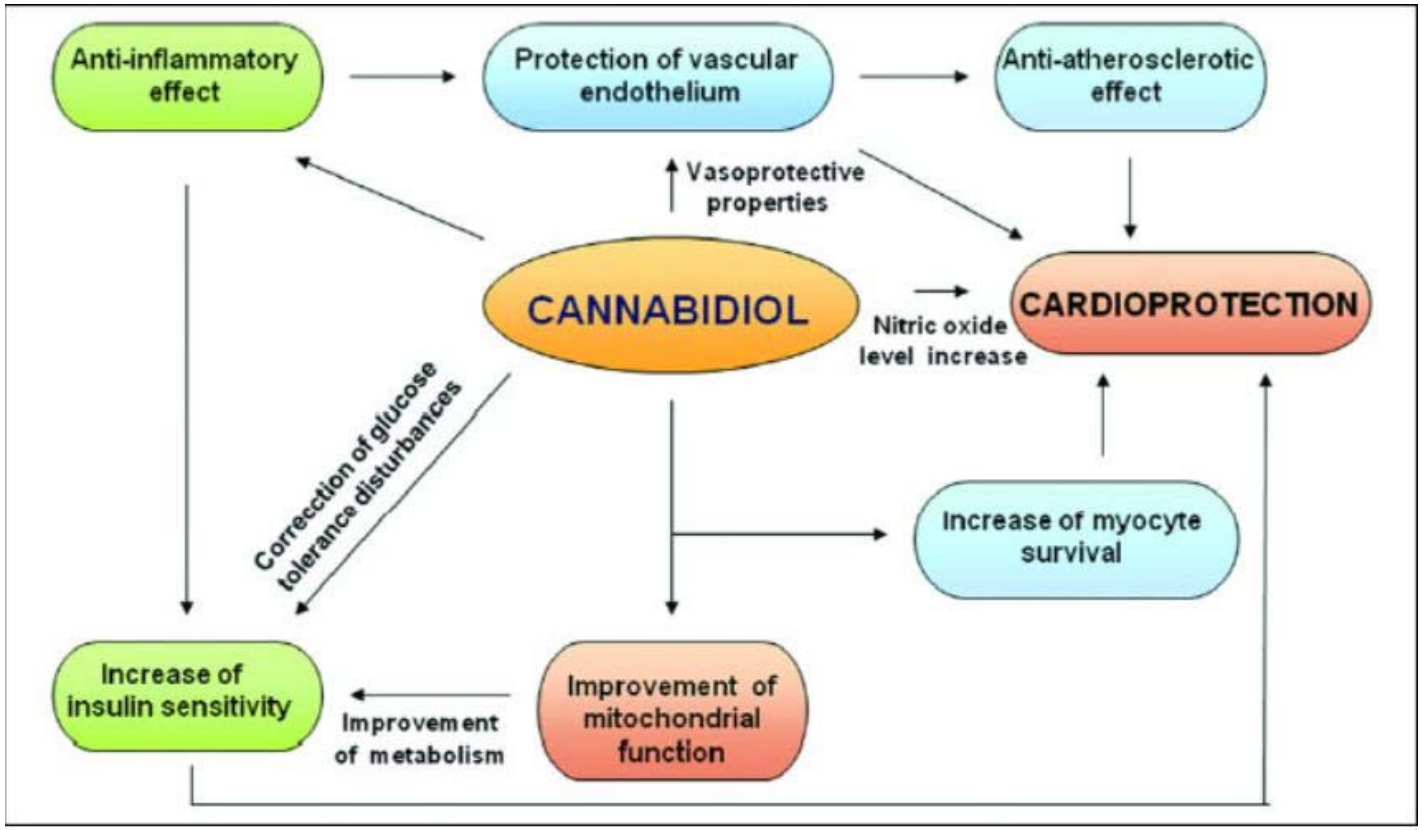
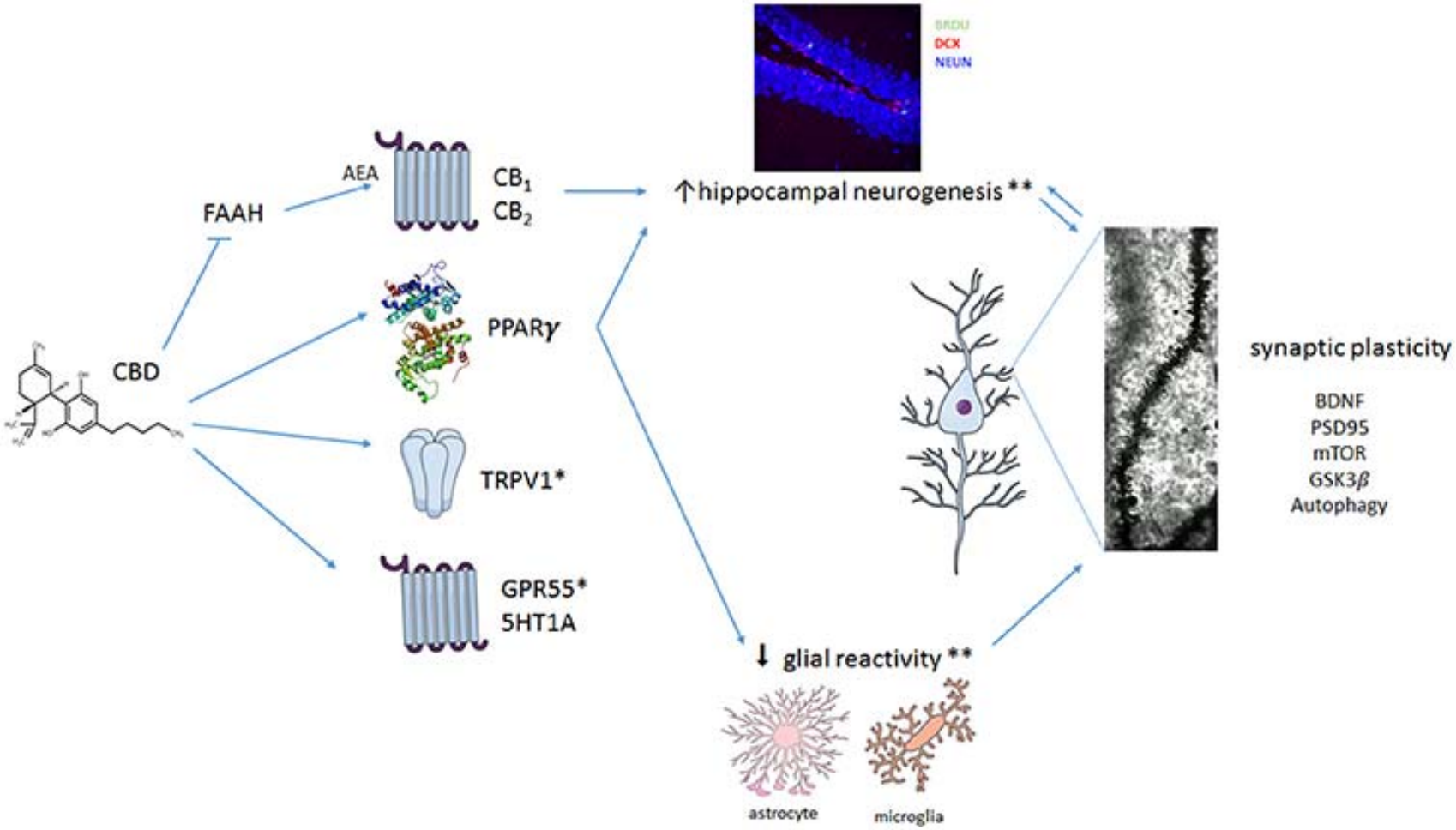


Fig. 3. Therapeutic potential targets of cannabidiol (CBD) in diabetes. CBD may exert beneficial effects against various diabetic complications by attenuating high glucose (inducing endothelial cell activation and inflammatory response), cardioprotection, increasing sensitivity to insulin, protection of vascular endothelium, improvement of metabolism, anti-inflammatory and anti-atherosclerotic effects.

Action of CBD on diabetes

Mechanism of Action (cont.)

CBD and neuroprotective mechanisms



Mechanism of Action (cont.)

CBD and neuroprotective mechanisms (cont.)

Main effect of CBD	Model	CBD Dose/concentration range	Route of administration	Species/Strain	Possible mechanism of action	References
Prevents NMDA receptor-induced excitoxicity	E17 cortical neurons culture	EC50 = 3.7 μM	*In vitro*	Wistar rat	Effect independent of cannabinoid receptors.	Hampson et al., 1998
↓Phosphorylated form of p38/MAP kinase, ↓Caspase 3 levels, and NFκ-b activation	β amyloid-induced neurotoxicity in PC12 cells	10 μM	*In vitro*	PC12 cells	Antioxidant	Esposito et al., 2006
Prevented gliosis, neuronal death and ↑ hippocampal neurogenesis	Genetic model of Alzheimer's Disease	10 mg/kg	15 days	C57BL6 mice	PPARγ	Esposito et al., 2011
↓Aβ cell viability and ↓LPS (conditioned media) induced microglia activation	β amyloid -induced neuronal toxicity in neuroblastoma cells. LPS-induced microglial-activation	10 μM	*In vitro*	Neuroblastoma (SH-SY5Y) cells/Microglial (BV-2) cells	Not determinated	Janefjord et al., 2014
Improved cell viability	Amyloid β -induced toxicity and tert-butyl hydroperoxide-induced oxidative stress	0.01–10 μM	15 min pre-incubation before Aβ or sAβ addition/ 24-h incubation for oxidative stress analysis	PC12 and Neuroblastoma (SH-SYS5) cells	Not determinated	Harvey et al., 2012
↓ Amyloid- β production	Amyloid β -induced neurotoxicity	100 nM	24 h	SHSY5Y (APP+) neurons	PPARγ	Scuderi et al., 2014
Reversed 3-nitropropionic acid—induced ↓ GABA contents, ↓ substance P, ↓ neuronal-specific enolase and superoxide dismutase(SOD)-2	(10 mg/kg) 3-nitropropionic acid-induced) striatal lesions	5 mg/kg	5 days, i.p.	Sprague-Dawley rats	Independent of CB_1, $TRPV_1$ and A_{2A} receptors	Sagredo et al., 2007
↓ Levels of IL-1beta, GFAP and iNOS	Amyloid β -induced neurotoxicity	10 mg/kg	i.p.	C57BL6 mice	Not determinated	Esposito et al., 2007
Reduced dopamine depletion and ↑mRNA levels of SOD in the substantia nigra	6-hydroxydopamine toxicity	3 mg/kg	14 days, i.p.	Sprague-Dawley rats	Antioxidant	Garcia-Arencibia et al., 2007
↓Cell death	H_2O_2-inducedoxidative stress in Oligodendrocyte progenitor cells	1 μM	*In vitro*	Oligodendrocyte progenitor cells	Not determinated	Mecha et al., 2012
↓of carbonyl groups and prevents the decrease in BDNF expression	Amphetamine-induced oxidative stress	60 mg/kg	2 weeks, i.p.	Wistar rats	Not determinated	Valvassori et al., 2011
↓ NFκ-B, ↓ ICAM-1 and VACAM-1	High glucose-induced mithocondrial superoxide	4 μM	*In vitro*	Human coronary artery endothelial cells	Independent from CB1 and CB2 receptors	Rajesh et al., 2007

Mechanism of Action (cont.)

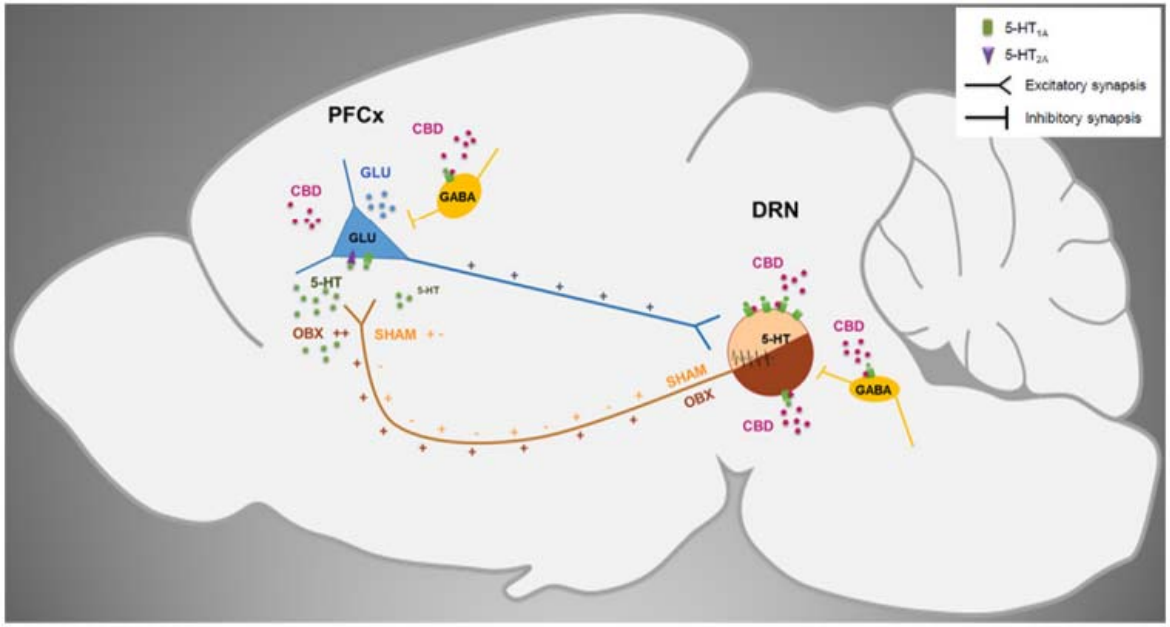
CBD and neuroprotective mechanisms (cont.)

Prevented Aβ-induced cognitive deficits, ↓ microglia activation, ↓ IL-6 mRNA expression Inhibited NO generation and ATP-induced intracellular Ca2+ levels	Rat primary cortical cultures, N13 and BV-2 microglial cells Morris water maze	10–1,000 nM	*In vitro* 3 weeks: first week treated daily; second and third weeks treated 3 times/week, i.p.	Rat primary cortical cultures, N13 and BV-2 microglial cells C57BL6 mice	Some of the *in vitro* effects were mediated by A_{2A}, CB_1, and CB_2 receptors	Martín-Moreno et al., 2011
Blocked LPS-induced STAT1 activation	LPS-induced BV-2 activation	10 μM	*In vitro*	BV-2 microglial cells	Not determinated	Kozela et al., 2010
↓Apoptosis; ↓Excitotoxicty and neuroinflamation	Newborn hypoxic-ischemic brain damage	0.1–1,000 μM	*Ex vivo*	Brain slices from C57BL6 mice	CB_2 and A_{2A} receptors	Castillo et al., 2010
Protects against the reduction in tyrosine hydroxylase activity	6-hydroxydopamine-induced toxicity in the striatum and substantia nigra	3 mg/kg	14 days, i.p.	Sprague-Dawley rats	Not determinated	Lastres-Becker et al., 2005
↑ Viable neurons and ↓ excitoxicity, oxidative stress, and inflammation	Newborn hypoxic-ischemic brain damage (HI)	1 mg/kg	30 min after HI, i.p.	Newborn pigs	CB_2 and $5HT_{1A}$ receptors	Pazos et al., 2013
Improve of cognition and motor activity. Restores BDNF levels	Encephalopathy (bile duct ligation)	5 mg/kg	28 days, i.p.	C57BL6 mice	$5HT_{1A}$	Magen et al., 2010
Improvments od liver function, normalizes 5-HT levels, and improves brain pathology	Encephalopathy (thioacetamide)	5 mg/kg	Single dose	C57BL6 mice	5HT-dependent mechanism	Avraham et al., 2011
Faciltates autophagic flux and decrease oxidative stress	Pilocarpine-Induced Seizure	100 ng	Intracerebroventricular	Wistar rats	Induction of autophagy pathway	Hosseinzadeh et al., 2016
Suppresses the transcription proinflammatory genes	MOG35-55-specific T cell in the presence of spleen-derived antigen presenting cells	5 μM	*In vitro*	MOG35-55- and APCs isolated from spleens of C57BL6	Not determinated	Kozela et al., 2016
Attenuates TNF-α production and ↓ adenosine transport	murine microglia and RAW264.7 macrophages LPS-treated mice	500 nM or 1 mg/kg	*In vitro*	Murine microglia	A_{2A} adenosine receptor	Carrier et al., 2006
			In vivo (1 h before LPS injection, i.p.)	RAW264.7 macrophages C57BL6 mice		
Improves motor deficits in the chronic phase; ↓ microglial activation and Il-beta and TNF-α production	Viral model of multiple sclerosis	5 mg/kg	7 days, i.p	SJL/J mice	A_{2A} adenosine receptor	Carrier et al., 2006
Normalizes synaptophyisin and caspase 3 expression	Brain damage induced by iron overload during neonatal period	Not informed	14 day, i.p.	Wistar rats	Not determinated	da Silva et al., 2014
Prevented MPP-induced toxicity and induces neurite growth	MPP-induced toxicity in PC12 cells and SH-SY5Y	1 μM	*In vitro*	PC12 and SH-SY5Y cells	TRKA	Santos et al., 2015
Prevents cognitive and anxiogenic effects, ↓ TNF-α and IL-6 ↑ BDNF levels	Murine model of cerebral Malaria	30 mg/kg	10 days, i.p.	C57BL6 mice	Not determinated	Campos et al., 2015

i.p., intra peritoneal; ↓, decreases; ↑, increases.

Mechanism of Action (cont.)

In prefrontal cortex, CBD would potentiate the **inhibitory function of 5-HT1A receptors** upon **GABAergic interneurons**, favouring glutamate signalling in postsynaptic areas, the stimulation of pyramidal descending projections to **DRN**, and therefore the neuronal **firing** of **serotonergic neurons**, and the 5-HT **increase** in **mPFCx**. In DRN, CBD would **increase** the **firing** of **serotonergic** neurons by **reducing** the **inhibitory effect** of **GABAergic** interneurons, without the detrimental effect of somatodendritic 5-HT1A receptors which are desensitised in OBX mice, therefore **leading to an increase in 5-HT levels in PFCx.**

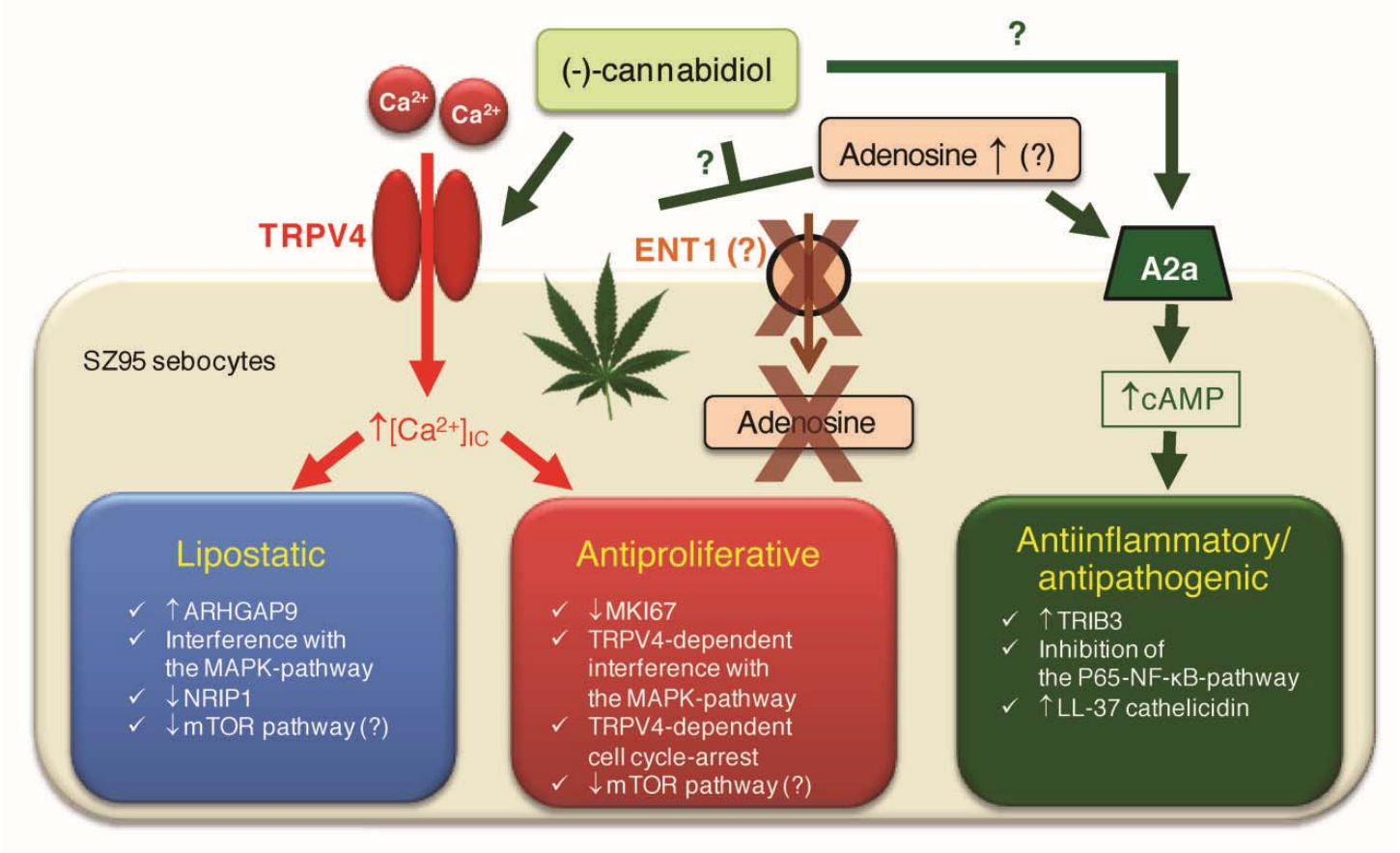


Proposed neurochemical mechanism of antidepressant effects

Linge, R., Jiménez-Sánchez, L., Campa, L., Pilar-Cuéllar, F., Vidal, R., Pazos, A., ... & Díaz, Á. (2016). Cannabidiol induces rapid-acting antidepressant-like effects and enhances cortical 5-HT/glutamate neurotransmission: role of 5-HT1A receptors. *Neuropharmacology*, *103*, 16-26.

Mechanism of Action (cont.)

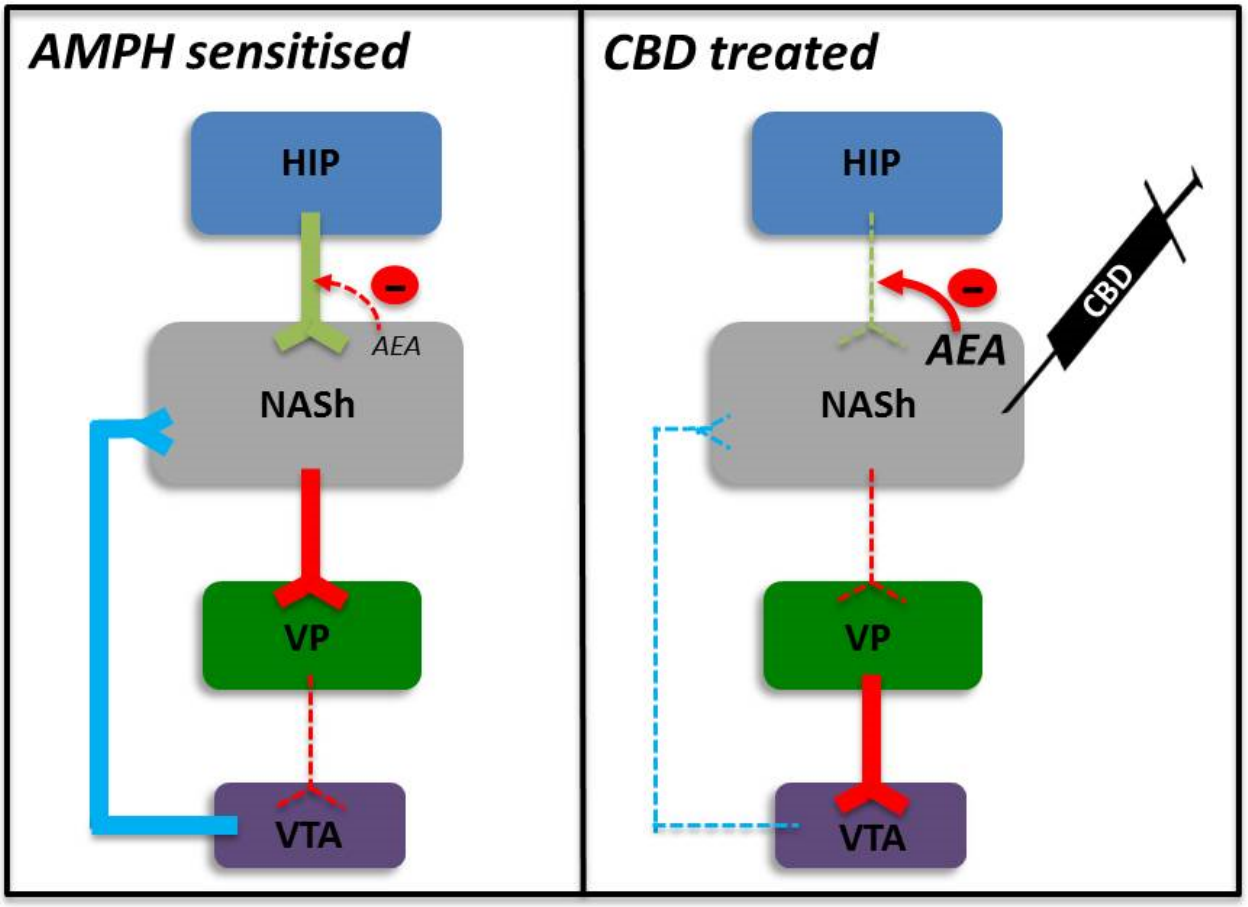
Schematic overview of the cellular "anti-acne trinity" of CBD and its proposed mechanism of action



Mechanism of Action (cont.)

A new antipsychotic mechanism of action for cannabidiol

In the AMPH sensitised state, increased firing of hippocampal (HIP) neurons leads to reduced ventral pallidum (VP)-inhibitory control of dopaminergic output from the ventral tegmental area (VTA). This results in an enduring increase in dopaminergic neurotransmission. Injections of cannabidiol (CBD) into the nucleus accumbens shell (NASh) increases synaptic levels of anandamide (AEA). AEA inhibits hippocampal output to the NASh and this leads to increased VP-inhibitory control of the VTA, thus normalising dopaminergic neurotransmission. Green line – glutamergic afferent, red line – GABA-ergic afferent, blue line – dopaminergic afferent.

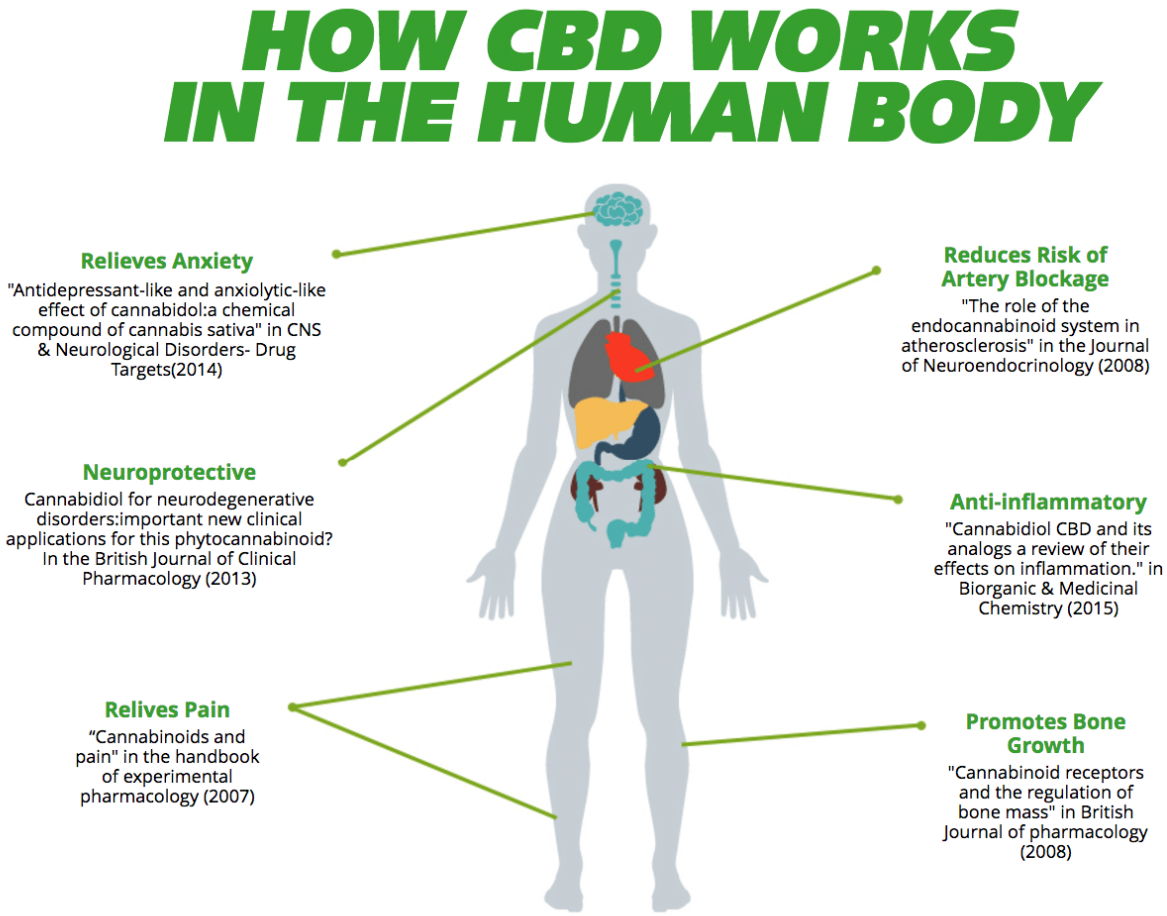


Mechanism of Action (cont.)

- Some evidence suggests that CBD **enhances the beneficial effects** of THC by **limiting its psychotropic** activity and thus **increasing its tolerability at higher doses**.
- This might be explained by research showing that **CBD counteracts CB1 activation in the brain**.
- This is further supported by the fact that **more psychotic symptoms** are reported in cannabis users who smoke preparations **with low CBD:THC ratios** as opposed to preparations with high CBD:THC ratios.

Picture from https://sensiseeds.com/en/blog/can-cbd-counteract-effects-thc/

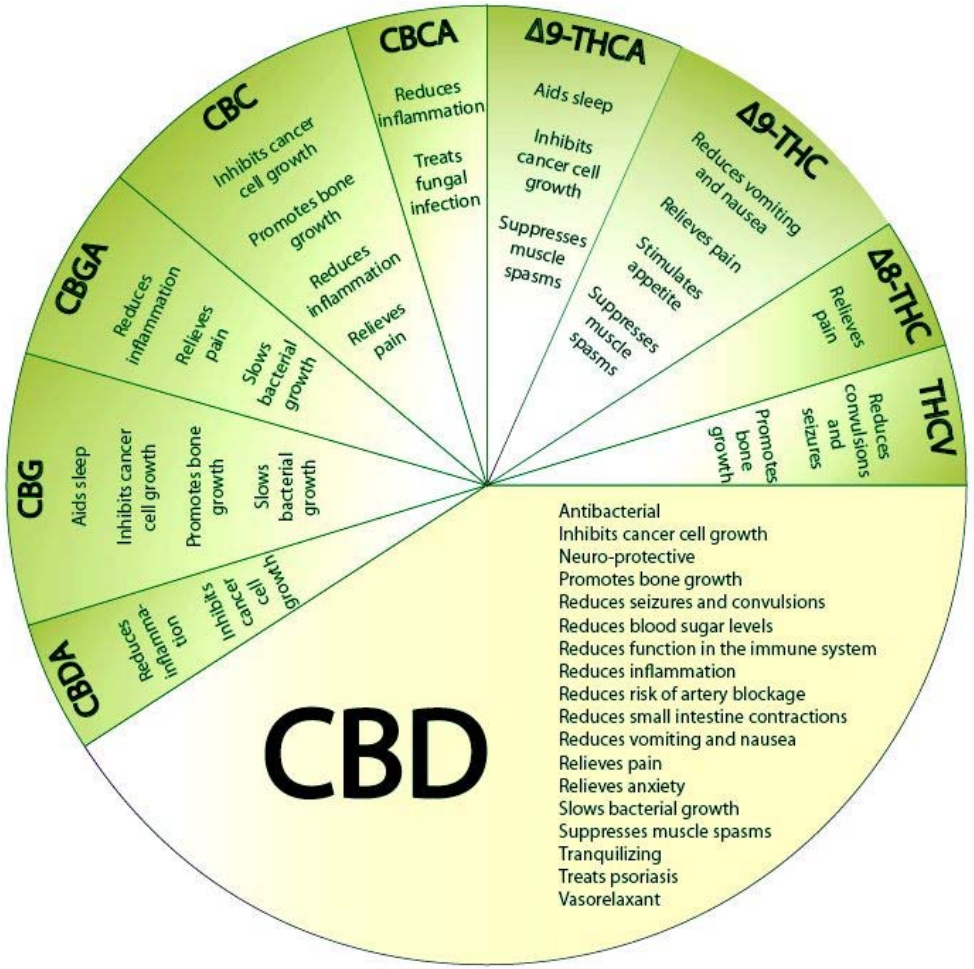
Mechanism of Action (cont.)



Picture from https://run-cbd.com/mechanism-action-cbd/

Medical Uses

- **Common Use**
- **Orally**, cannabidiol is used for
  - **anxiety**
  - **bipolar disorder**
  - **dystonia**
  - **epilepsy**
  - **multiple sclerosis**
  - **Parkinson's disease**
  - **schizophrenia**
- **Inhaled**
  - **smoking cessation**

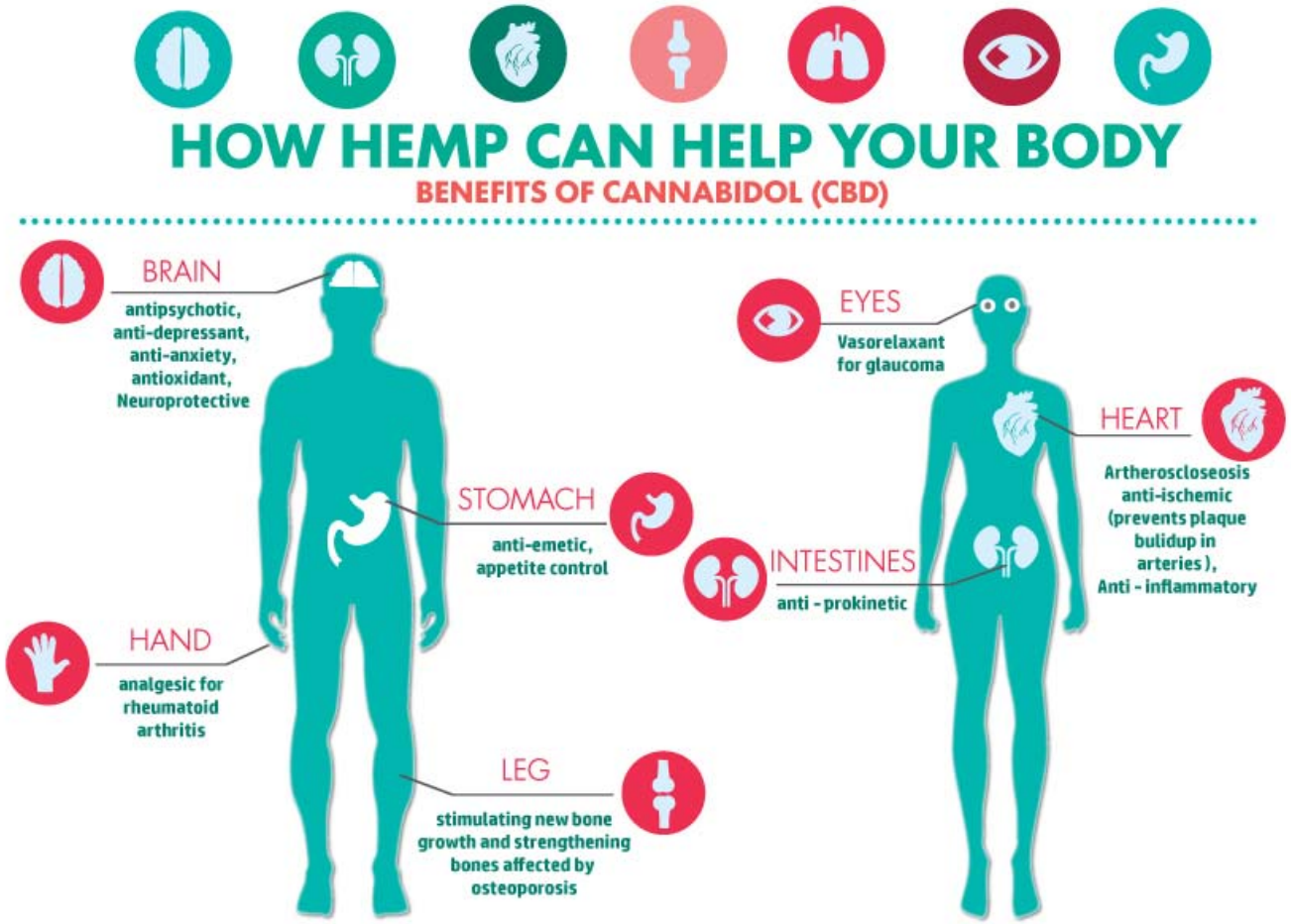


Medical Uses (cont.)

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

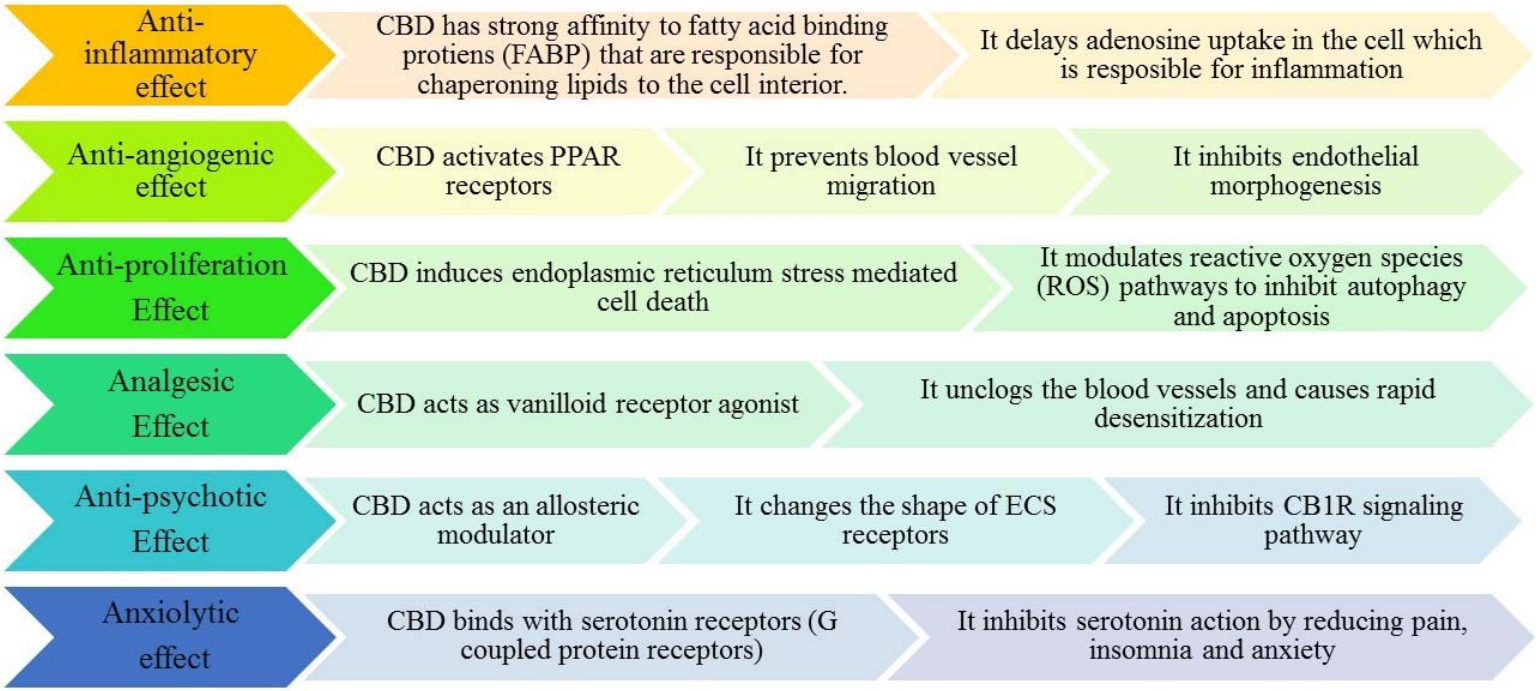
Picture from
https://www.cannabiscure.info/wp-content/uploads/2016/07/Health-benefits-cannabis.png

Medical Uses (cont.)



Picture from http://cbdhealthfirst.com/health-benefits/

Medical Uses (cont.)



Picture from:

Therapeutic properties of Cannabidiol. Information collected from the following souces. (Bisogno et al., 2001; de Mello Schier et al., 2014; Devinsky et al., 2014; Hernán Pérez de la Ossa et al., 2013; Massi, Solinas, Cinquina, & Parolaro, 2013; Mechoulam, Parker, & Gallily, 2002; Savonenko et al., 2015; Shrivastava, Kuzontkoski, Groopman, & Prasad, 2011; M Solinas et al., 2012; Turner et al., 2017; Zuardi, Crippa, Hallak, Moreira, & Guimaraes, 2006)

Safety - Dosing

- **Oral:**
  - **Dystonia**: 100-600 mg daily for 6 weeks has been used.
  - **Epilepsy**: 200-300 mg daily for up to 18 weeks has been used
  - **Insomnia**: 160 mg 30 minutes before bed has been used
  - **Multiple sclerosis:** sublingual spray delivering 2.5 mg cannabidiol per actuation, with a maximum dosing of 120 mg per 24 hours, has been used
  - **Parkinson's disease:** 150 mg daily, with weekly dose escalations of 150 mg as needed, for 4 weeks has been used for psychosis in Parkinson's disease
  - **Schizophrenia:** 400 mg four times daily for 4 weeks has been used
  - **Social anxiety disorder:** Single doses of cannabidiol 400-600 mg have been used for anxiety related to public speaking or medical imaging
- **Inhalation**:
  - **Smoking cessation:** Metered dose inhalers delivering cannabidiol 400 mcg per actuation, used as needed for one week, have been used

Safety – ADR

- **Cannabidiol** has been **well-tolerated** in most clinical trials to date.
- Some adverse effects reported with oral cannabidiol include
  - **dry mouth**
  - **Hypotension**
  - **Lightheadedness**
  - **orthostatic hypotension**
  - **psychomotor slowing, sedation**
  - **somnolence**

- **Cardiovascular**
  - Orally, cannabidiol has caused hypotension, orthostatic hypotension, and lightheadedness in some patients in one clinical study. However, other research suggests that taking cannabidiol orally does not significantly change blood pressure or heart rate compared to placebo.
- **Gastrointestinal**
  - Orally, cannabidiol has cause dry mouth in some patients in clinical research
- **Neurologic/CNS**
  - Some preliminary clinical research suggests that cannabidiol might cause sedation and psychomotor slowing in some patients when taken orally. Somnolence has also been reported with cannabidiol use

Safety – Toxicity

- The median lethal dose (LD50) of intravenous (IV) cannabidiol in rhesus **monkeys** is **212 mg/kg**.
- While the LD50 of oral cannabidiol has not been established, oral doses of cannabidiol **20-50 times** larger than intravenous doses are required to elicit severe intoxication in animals, suggesting that the LD50 of oral cannabidiol is much larger than the LD50 of IV cannabidiol
- Cannabidiol has been shown to **decrease testicular weight** and **testicular testosterone levels** in **mice.**
- Additionally, oral treatment with cannabidiol **30-300 mg/kg** has been shown to **decrease testicular size and inhibit spermatogenesis** in **monkeys**.
- Preliminary clinical research in **humans** suggests that cannabidiol **does not have mutagenic effects**.

Safety – H (Herbal)D(Drug)Interaction

CNS DEPRESSANTS
- Moderate

Cytochrome P450 1A1 (CYP1A1) Inhibitors
- Moderate

Cytochrome P450 1A2 (CYP1A2) Inhibitors
- Moderate

Cytochrome P450 2C19 (CYP2C19) Inhibitors
- Moderate

Cytochrome P450 2C9 (CYP2C9) Inhibitors
- Moderate

Cytochrome P450 2D6 (CYP2D6) Inhibitors
- Moderate

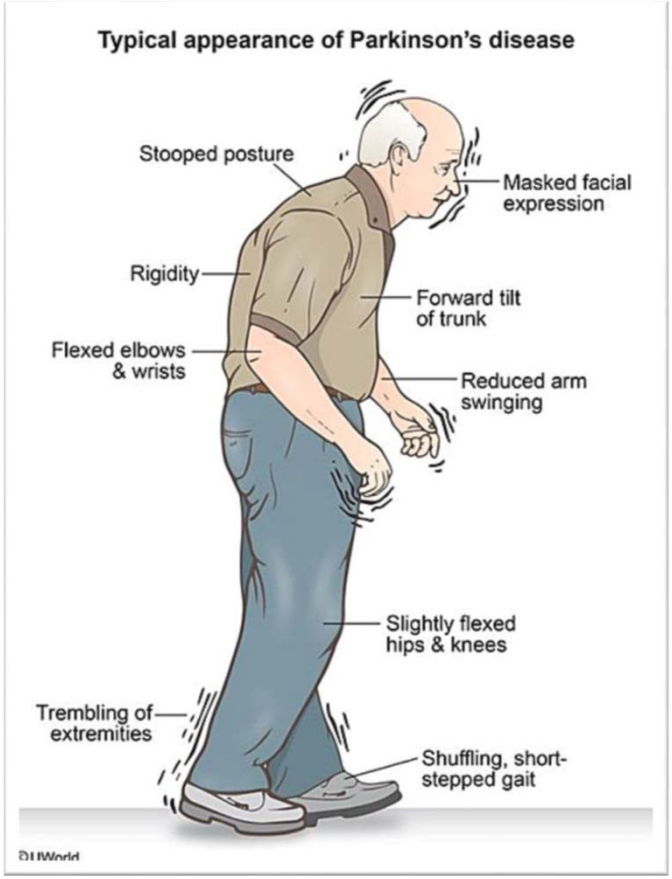
Cytochrome P450 3A4 (CYP3A4) Inhibitors
- Moderate

Safety – H(Herbal)H(Herbal)Interaction

- **HERBS AND SUPPLEMENTS WITH SEDATIVE PROPERTIES**
  - Preliminary clinical research and animal studies suggest that high dose cannabidiol has **sedative and hypnotic effects.** Theoretically, concomitant use of cannabidiol with herbs and supplements with **sedative properties** might **enhance therapeutic and adverse effects**.
  - Such as
    - **Calamus**
    - **California poppy**
    - **Catnip**
    - **Hops**
    - **Jamaican dogwood**
    - **Kava**
    - **L-tryptophan**
    - **Melatonin**
    - **Sage**
    - **SAMe**
    - **St. John's wort**
    - **Sassafras**
    - **skullcap**

Safety – Interactions with Diseases

- **PARKINSON'S DISEASE**
  - Orally, cannabidiol may **worsen symptoms of Parkinson's disease** in some patients.
    - Preliminary clinical research shows that taking cannabidiol 300 mg or more daily exacerbates hypokinesia and resting tremor in some patients with Parkinsonian features



PK Data

Absorption

- Animal research suggests that oral cannabidiol is poorly absorbed, with a bioavailability between 13% to 19%. This is likely due to a significant first-pass effect. In humans, the bioavailability of inhaled cannabidiol ranges from 11% to 45%. However, inhaled cannabidiol bioavailability > 65% has been reported when using a specific cannabidiol metered dose inhaler (STI Pharmaceuticals: Brentwood, UK). Taking oral cannabidiol 10 mg/kg/day long-term results in mean plasma concentrations of 5.9-11.2 ng/mL in humans

Distribution

- Animal research shows that cannabidiol is rapidly distributed upon intravenous administration.

PK Data (cont.)

Metabolism

- Similar to other cannabinoids, cannabidiol undergoes hydroxylations, oxidations, beta-oxidation, conjugation, and epoxidation. Conjugation with fatty acids increases its lipophilicity and ability to accumulate in tissues

Excretion

- Cannabidiol has a terminal half-life of around 9 hours in dogs. Clinical research suggests that the half-lives of inhaled and intravenous cannabidiol are 31 hours and 24 hours, respectively. Cannabidiol is primarily excreted in the urine unchanged and as a glucuronide metabolite.

Effectiveness and Clinical Studies

INSUFFICIENT RELIABLE EVIDENCE to RATE!

Indication	Description	Studies	Evaluation
Bipolar disorder	Preliminary case reports suggest that taking cannabidiol 600-1200 mg/day orally for 25 days does not improve manic episodes in patients with bipolar disorder	Zuardi A, Crippa J, Dursun S, et al. Cannabidiol was ineffective for manic episode of bipolar affective disorder. J Psychopharmacol 2010;24(1):135-7. View abstract.	Controlled clinical trials are necessary to further examine cannabidiol's effect in bipolar disorder.
Dystonia	Preliminary clinical research suggests that cannabidiol 100-600 mg daily for 6 weeks improves dystonia by 20% to 50% in some patients with Meige's syndrome, levodopa-induced dystonia, or primary dystonia	Consroe P, Sandyk R, Snider SR. Open label evaluation of cannabidiol in dystonic movement disorders. Int J Neurosci 1986;30(4):277-82. View abstract	A lack of adequate control limits the validity of these findings.

Effectiveness and Clinical Studies (cont.)

INSUFFICIENT RELIABLE EVIDENCE to RATE!

Indication	Description	Studies	Evaluation
Epilepsy	While some preliminary clinical research suggest that cannabidiol 200-300 mg daily for up to 18 weeks might reduce seizures in some patients, other research shows that cannabidiol 100-300 mg daily for up 6 months does not reduce seizure frequency in patients with epilepsy	1. Ames, F. R. and Cridland, S. Anticonvulsant effect of cannabidiol. S.Afr.Med.J. 1-4-1986;69(1):14. View abstract. 2. Cunha, J. M., Carlini, E. A., Pereira, A. E., Ramos, O. L., Pimentel, C., Gagliardi, R., Sanvito, W. L., Lander, N., and Mechoulam, R. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology 1980;21(3):175-185. View abstract. 3. Trembly B, Sherman M. Double-blind clinical study of cannabidiol as a secondary anticonvulsant. Marijuana '90 International Conference on Cannabis and Cannabinoids 1990;2:5.	All studies examining cannabidiol for epilepsy are currently limited by a small sample size.
Huntington's disease	Preliminary clinical research shows that cannabidiol 10 mg/kg daily does not improve chorea severity or other symptoms compared to placebo in patients with Huntington's disease	Consroe, P., Laguna, J., Allender, J., Snider, S., Stern, L., Sandyk, R., Kennedy, K., and Schram, K. Controlled clinical trial of cannabidiol in Huntington's disease. Pharmacol Biochem.Behav. 1991;40(3):701-708. View abstract.	

Effectiveness and Clinical Studies (cont.)

INSUFFICIENT RELIABLE EVIDENCE to RATE!

Indication	Description	Studies
Insomnia	Preliminary clinical research suggests that cannabidiol 160 mg before bed significantly improves sleep duration compared to placebo in patients with insomnia. However, lower doses of cannabidiol (40 mg and 80 mg) do not have this effect. Cannabidiol is not associated with a next morning "hangover" effect. However, it does not seem to improve sleep induction and may reduce dream recall in some patients	Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. J Clin Pharmacol 1981;21(8-9 Suppl):417S-27S. View abstract.
Multiple sclerosis (MS)	There is inconsistent evidence regarding the effect of cannabidiol on symptoms of multiple sclerosis. Preliminary clinical research suggests that administration of a sublingual cannabidiol spray delivering cannabidiol 2.5 mg per actuation, with a maximum dosing of 120 mg per 24 hours, might improve self-reported pain and muscle spasm severity compared to placebo in patients with multiple sclerosis and other neurogenic symptoms. However, it does not appear to improve muscle spasm frequency, fatigue, bladder control, mobility, quality of life, or general well-being in these patients. Also, sublingual cannabidiol spray does not appear to improve muscle spasms when assessed using the more objective Ashworth scale score	Wade, D. T., Robson, P., House, H., Makela, P., and Aram, J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin.Rehabil. 2003;17(1):21-29. View abstract.

Effectiveness and Clinical Studies (cont.)

INSUFFICIENT RELIABLE EVIDENCE to RATE!

Indication	Description	Studies	Evaluation
Parkinson's disease.	Some preliminary clinical research shows that taking flexible-dose cannabidiol, starting at 150 mg daily for 4 weeks significantly improves psychotic symptoms compared to baseline in Parkinson's disease patients with psychosis	1. Zuardi AW, Crippa JA, Hallak JE, et al. Cannabidiol for the treatment of psychosis in Parkinson's disease. J Psychopharmacol 2009;23(8):979-83.View abstract.	A lack of adequate control limits the validity of these findings
Schizophrenia	Case reports show inconsistent results. Some preliminary clinical research suggests that cannabidiol 400 mg four times daily for 4 weeks significantly improves psychotic symptoms compared to baseline and may be as effective as the antipsychotic amisulpride in patients with schizophrenia. However, other preliminary research suggests that taking cannabidiol for 14 days is no more effective than placebo for treating psychotic symptoms in schizophrenic patients.	1. Zuardi AW, Morais SL, Guimaraes FS, Mechoulam R. Antipsychotic effect of cannabidiol. J Clin Psychiatry 1995;56(10):485-6. View abstract. 2. Zuardi AW, Hallak JE, Dursun SM, et al. Cannabidiol monotherapy for treatment-resistant schizophrenia. J Psychopharmacol 2006;20(5):683-6.View abstract. 3. Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry 2012;2:e94. View abstract. 4. Leweke FM, Kranaster L, Pahlisch F, et al. The efficacy of cannabidiol in the treatment of schizophrenia - a translational approach. Schizophr Bull 2011;37(Suppl 1):313.	Evidence on the use of cannabidiol for psychotic symptoms in schizophrenia has been mixed These differences might be explained by variances in cannabidiol dose and study duration.

Effectiveness and Clinical Studies (cont.)

INSUFFICIENT RELIABLE EVIDENCE to RATE!

Indication	Description	Studies	Evaluation
Smoking cessation	Preliminary clinical research suggests that use of an inhaler delivering cannabidiol 400 mcg per actuation for one week might reduce number of cigarettes smoked by around 40% compared to baseline in some patients.	Morgan CJ, Das RK, Joye A, et al. Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings. Addict Behav 2013;38(9):2433-6. View abstract.	It is still unclear if cannabidiol is significantly superior to placebo
Social phobia	Some preliminary clinical research shows that cannabidiol 300 mg does not improve anxiety compared to placebo or diazepam in patients with social phobia undergoing a simulated public speaking test. However, other preliminary clinical research suggests that taking a higher dose of cannabidiol 600 mg significantly improves anxiety compared to placebo in patients with social phobia undergoing a similar simulated public speaking test. Additional preliminary research suggests that taking cannabidiol 400 mg significantly improves anxiety compared to placebo in patients with social phobia undergoing single photon emission computed tomography (SPECT) imaging.	1. Crippa JA, Derenusson GN, Ferrari TB, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J Psychopharmacol 2011;25(1):121-30. View abstract. 2. Bergamaschi MM, Queiroz RH, Chagas MH, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. Neuropsychopharmacology 2011;36(6):1219-26. View abstract. 3. Zuardi AW, Cosme RA, Graeff FG, Guimaraes FS. Effects of ipsapirone and cannabidiol on human experimental anxiety. J Psychopharmacol 1993;7(1 Suppl):82-8. View abstract.	

Recent Studies

- CBD is suitable to treat patients with refractory epilepsy, especially children with **Dravet, Lennox-Gastaut or West syndrome**. Article on the use of cannabis to treat epilepsy for further information on this subject. Our article includes many studies from plenty of sources, such as Dr. Devinsky's study published in March 2014 in the Epilepsy journal.

Clinical Trials of cannabidiol in epilepsy

Study	Treatments (subjects per group)	Duration	Outcome	Toxicity	Limitations
Mechoulam and Carlini, (1978)[72]	TRE– CBD 200 mg/day (4) TRE– Placebo (5)	3 months	CBD: 2 seizure free; 1 partial improvement; 1 no change	None	No baseline seizure frequency, no definition of improvement; unclear if AEDs were changed; small N/limited power; not truly randomized-blinded; unknown if groups were matched
Cunha et al. (1980)[73]	TRE-TLE CBD (7)[a] TRE-TLE Placebo (8)[a,b]	200–300 mg/day for 3–18 weeks	Last visit: 4 CBD, 1 placebo	Somnolence	Not clearly blinded, since one patient transferred groups and doses were adjusted in CBD, but no mention of this in placebo group and CBD group received had longer average treatment
Ames and Cridland (1986)[74]	IDD-TRE CBD (?6)[c] IDD-TRE Placebo (?6)[c] × 4 weeks	CBD 300/day × 1 week; 200/day × 3 weeks	No difference between CBD v. Placebo	Somnolence	This was a letter to the editor and details are lacking
Trembly and Sherman (1990)[75]	TRE (?10 or 12)[d]	3 months baseline; 6 months placebo: Randomized to either 6 months placebo v. CBD 100 t.i.d.; then crossover for 6 months on alternative treatment	No change in seizure frequency or cognitive/ behavioral tests	None	Only truly double blind study. Unclear why sample size differed in two reports. Data reported is incomplete

TRE, treatment-resistant epilepsy; TLE, temporal lobe epilepsy; IDD, intellectual/developmental disability.
[a]Frequent convulsions for ≥1 year; ~ 1 GTCSz per week.
[b]One patient transferred from placebo to treatment after 1 month.
[c]12 subjects were divided into two groups, but distribution uncertain.
[d]Abstract and subsequent book chapter have different N's (10 and 12).

Recent Studies (cont.)

- Cannabidiol has also been shown to have **antipsychotic properties**, mostly used to combat **schizophrenia**:
  1. Could cannabidiol be used as an alternative to antipsychotics? Published in the Journal of Psychiatric Research in March 2016.
  2. A systematic review of the antipsychotic properties of cannabidiol in humans, published in the Schizophrenia Research journal in February 2015.
  3. Cannabidiol as a potential treatment for psychosis, published in the European Neuropsychopharmacology journal in November 2013.
  4. A Critical Review of the Antipsychotic Effects of Cannabidiol: 30 Years of a Translational Investigation, published in the Current Pharmaceutical Design journal in June 2012.

Recent Studies (cont.)

- **Anxiety and depression:**
  - CBD is a very effective anxiolytic which improves mood and avoids depressive phases, as shown in the following studies:
    1. Cannabidiol induces rapid-acting antidepressant-like effects, published in the Neuropharmacology journal in October 2015.
    2. Cannabidiol as a Potential Treatment for Anxiety Disorders, published in the Journal of the American Society for Experimental NeuroTherapeutics in September 2015.
    3. Antidepressant-Like and Anxiolytic-Like Effects of Cannabidiol, published in the CNS & Neurological Disorders journal in 2014.
    4. Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug, published in the Revista Brasileira de Psiquiatria in June 2012.

Recent Studies (cont.)

- **Nausea and vomiting:**
  - Another property of Cannabidiol is being an **effective antiemetic**, as shown in this study published in August 2011 in the British Journal of Pharmacology. CBD is particularly efficient when used to combat nausea caused by chemotherapy according to this study published in December 2010 in the British Journal of Pharmacology.
- **Chronic inflammatory bowel diseases:**
  - The efficacy of CBD to treat chronic inflammatory bowel diseases is also being studied, like its application to combat **Crohn or ulcerative colitis diseases**.
    - Cannabidiol in Inflammatory Bowel Diseases: A Brief Overview, published in the Phytotherapy Research journal in May 2013.
    - Cannabidiol Reduces Intestinal Inflammation through the Control of Neuroimmune Axis, published in the Plos ONE journal in December 2011.

Recent Studies (cont.)

- **Multiple sclerosis:**
  - CBD is one of the active ingredients of **Sativex**, a medicine prescribed to multiple sclerosis patients. Furthermore, and according to a study published in January 2016 in the **DARU Journal of Pharmaceutical Sciences**, the use of CBD creams and ointments is also useful to treat this disease.
- **Acne:**
  - Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes, which means that it is also efficient to treat **acne and other skin problems**. This study was published in the Journal of Clinical Investigation in July 2014.
  - Moreover, another study published in the Experimental Dermatology journal in April 2016 shows that **CBD, CBDV, CBC and THCV** are efficient cannabinoids to treat acne, a disease that affects mostly teenagers, but also adults.

Recent Studies (cont.)

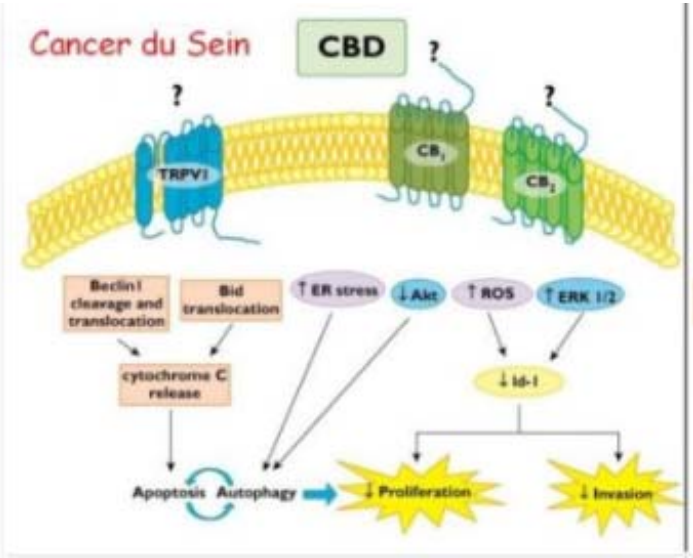
- **Neurological and neuropsychiatric conditions:**
  - Cannabidiol **protects neurons from degeneration**, which is especially useful when treating neurological diseases. This subject was already discussed in our article about cannabis and Alzheimer, in which you can view different studies such as the publication in February 2011 in the Molecular Pharmacology journal.
  - These **properties of CBD** are also being studied to treat other neurological conditions:
  - Cannabidiol, neuroprotection and neuropsychiatric disorders, published in the Pharmacological Research journal in February 2016.
  - Cannabidiol in Medicine: A Review of its Therapeutic Potential in CNS Disorders, published in the Phytotherapy Research journal in October 2008.

Recent Studies (cont.)

- **Drug addictions:**
  1. A study published in May 2015 in the Substance Abuse: Research and Treatment journal showed that Cannabidiol can be used to treat **addictive behaviors**.
  2. Another sudy published in April 2013 in the Addictive Behaviors journal claims that CBD would be particularly efficient to help people to **stop smoking tobacco**. It can also be used to reduce resistance to **opiates**, as demonstrated in this study published in the Neurotherapeutics journal in October 2015.
- **Fracture reconstructions:**
  - According to this study published in March 2015 in the Journal of Bone and mineral research, Cannabidiol CBD accelerates the recovery from **bone fractures** by stimulating the osteoblasts activity.

Recent Studies (cont.)

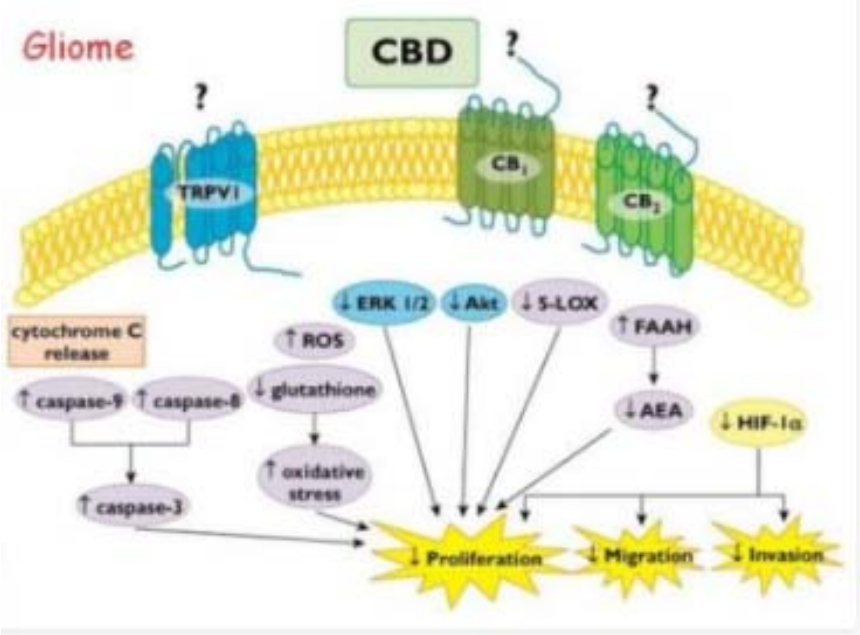
- **Cancer:**
  - CBD is one of the most efficient cannabinoids to treat some types of cancer, and its **anti-tumor action** is being currently studied. According to a study published in the British Journal of Pharmacology in May 2012, CBD acts as **angiogenesis inhibitor** by blocking the growth of different tumors *in vitro* and *in vivo.*



Effect of CBD in different tumor cells

Recent Studies (cont.)

- **Cancer:**
  - In the article about cannabis and cancer you can check several studies about the action of **CBD and other cannabinoids** on different types of tumors. We must mention that the CBD dosages used in these studies are far higher than those found in **hemp extracts** on the market today.



Effect of CBD in different tumor cells

Recent Studies (cont.)

- **Liver protection:**
  - **CBD prevents fatty liver syndrome** caused by alcohol consumption, as shown in a study published in the Free Radical Biology & Medicine journal in March 2014.
  - This protective action is not limited to alcohol but also **protects the liver from cocaine consumption**, according to a study published in the Mediators of Inflammation journal in April 2015.
- **Diabetes:**
  - If we take a look at this study on mice published in the Autoimmunity journal in April 2016, we realize that Cannabidiol could **reduce the impact of diabetes**. Moreover, CBD could also be useful to treat different conditions related to this disease, like cardiomyopathy or diabetic retinopathy.

Reference

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