CBD – HOPE AND/OR HYPE?

SAPhS
Swiss Academy
of Pharmaceutical
Sciences

Gregor Zorn

STCM 3.0 Confernce– 19.1.2019 – Bern, CH

Cannabidiol (CBD)

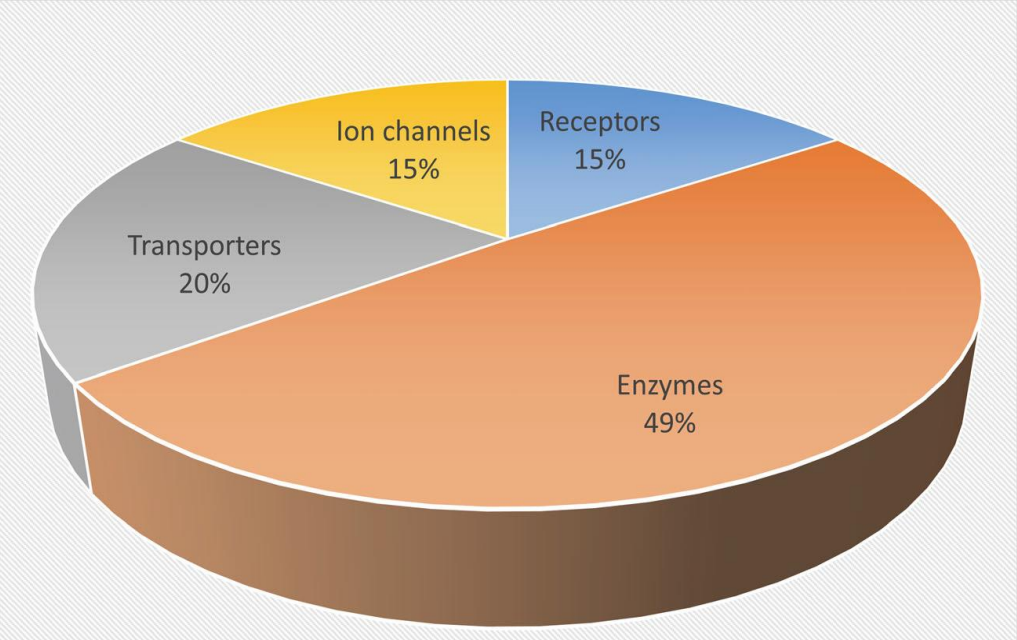
- Isolated 1940 (*Adams, 1940*),
- Structure identified in 1963 (*Mechoulam and Shvo, 1963)*
- Major cannabinoid in hemp (*CBDA*)
- New high-CBD cultivars with higher % of CBD 10-20%
- Beneficial effects and therapeutic potential

Cannabidiol (CBD)

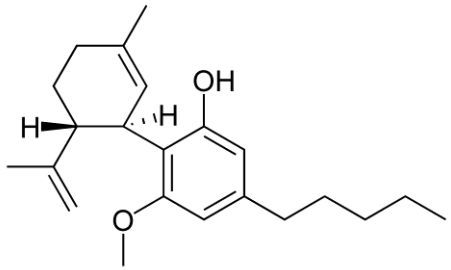
Non-intoxication

Poor affinity with cannabinoid receptors

- CB1- negative allosteric modulator (*Laprairie et al., 2015*)
- CB2 – partial agonist (*Tham et al., 2018*)



- Receptors: Adenosien, Opiod, Glycine, Serotonin, GPR55, GPR18
- Enzymes: CYP450, Phospholipase, FAAH, Arylalkylamine N-Acetyltransferase, Cyclooxygenases, Lipoxygenases, Indoleamine-2,3-dioxygenase
- Ion channels: TRPA1,TRPM8, TRPV1,2,3,4, VDAC1, Cav3.1,2,3 T-type
- Transporters: Neurotransmitter, Anandamide, Multidrug Resistance, Mg-ATPase



Ibeas Bih et al., 2015

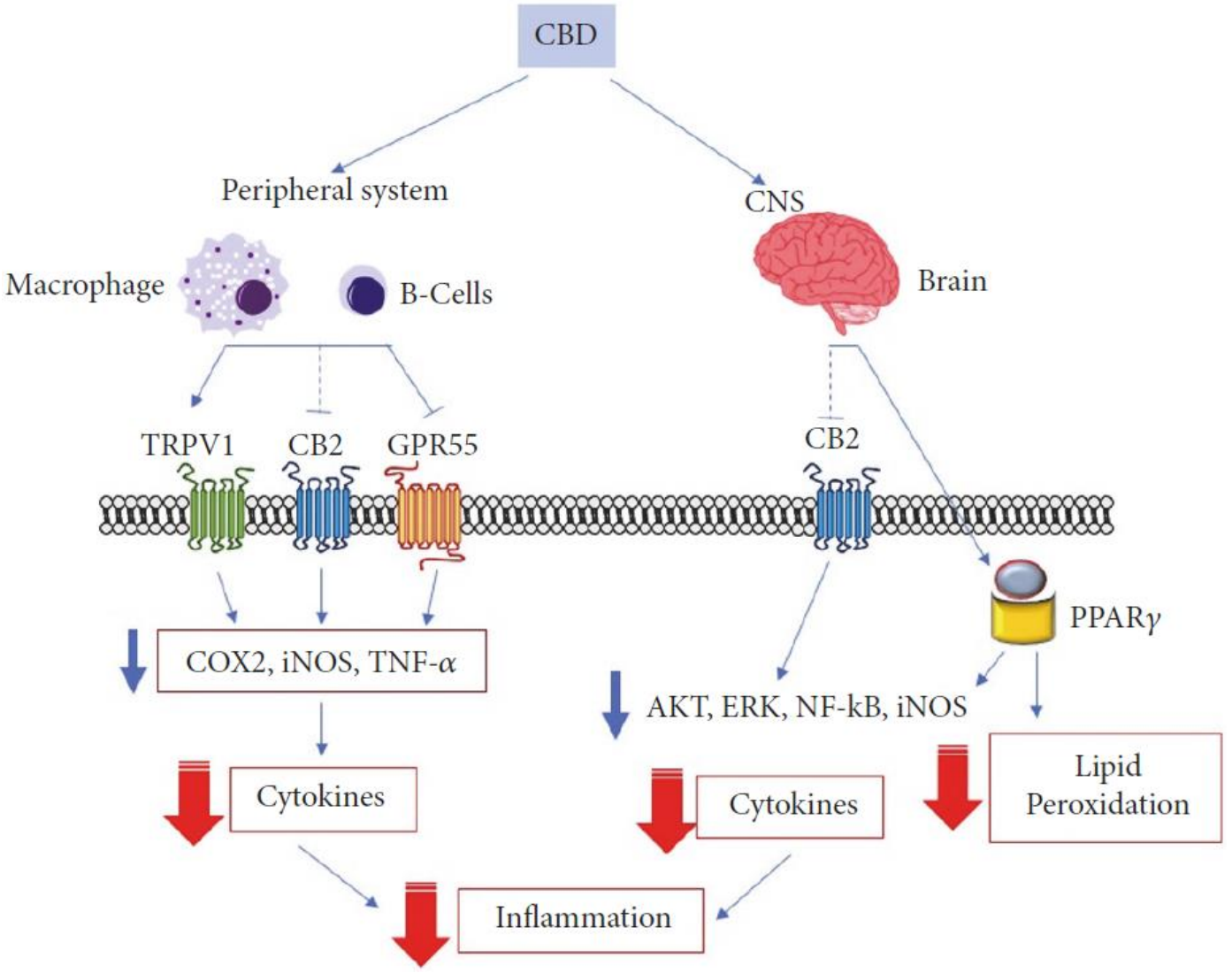
Cannabidiol (CBD)

- Analgesic (*Xiong et al., 2012*)
- Anti-inflammatory (*Carrier et al., 2006*)
- Neuroprotective, Neuroregenerative (*Hofmann & Frazier, 2013*)
- Antioxidant (*Hampson et al., 1998*)
- Antineoplastic (*Ligresti et al., 2006*)
- Antiemetic (*Limebeer et al., 2009*)
- Anxiolytic, antipsychotic (*Resstel et al., 2009*)
- Immunomodulator (*Yeshurun et al., 2015*)
- Antiepileptic (*Jones et al., 2010*)
- Bone growth stimulant (*Kogan et al., 2015*)

Pisanti et al., 2017

CBD anti-inflammatory effects

- **CBD anti-inflammatory effects in peripheral systems mediated via TRPV1, CB2, and GPR55 receptors** > downregulation of enzymes involved in the production of prostaglandins, reactive oxygen species, and cytokines
- **CBD anti-inflammatory effects in CNS mediated via CB2 and PPARγ receptors** > MAPK inhibition and NF-kB downregulation, PPARγ-mediated reduction of lipid peroxidation



Pellati et al., 2018

Inflammation

Inflammation is a complex defense mechanism against biological and chemical insults

Although beneficial, persistent inflammation can cause cellular damage resulting in many diseases including:

- Obesity, diabetes, Inflammatory bowel disease
- Schizophrenia, anxiety, depression
- Parkinson's Disease, Alzheimer's Disease, aging
- Cancer - it is estimated that about 15–20% of all cancer cases are preceded by chronic inflammation, including lung, colon and pancreatic cancers

Nutrients **2018**, *10*(5), 604; doi:10.3390/nu10050604

Open Access

Review

Inflammation, not Cholesterol, Is a Cause of Chronic Disease

Alexandros Tsoupras, **Ronan Lordan** and **Ioannis Zabetakis** *

Department of Biological Sciences, University of Limerick, V94 T9PX Limerick, Ireland

* Author to whom correspondence should be addressed.

Received: 23 April 2018 / Accepted: 9 May 2018 / Published: 12 May 2018

Plasma Biomarkers of Inflammation, the Kynurenine Pathway, and Risks of All-Cause, Cancer, and Cardiovascular Disease Mortality: The Hordaland Health Study

Hui Zuo, Per M. Ueland, Arve Ulvik, Simone J. P. M. Eussen, Stein E. Vollset, Ottar Nygård, Øivind Midttun, Despoina Theofylaktopoulou, Klaus Meyer, Grethe S. Tell

American Journal of Epidemiology, Volume 183, Issue 4, 15 February 2016, Pages 249–258, https://doi.org/10.1093/aje/kwv242

Published: 27 January 2016 **Article history**

Inflammation

Inflammation is a complex defense mechanism against biological and chemical insults

Although beneficial, persistent inflammation can cause cellular damage resulting in many diseases including:

- Obesity, diabetes, Inflammatory bowel disease
- Schizophrenia, anxiety, depression
- Parkinson’s Disease, Alzheimer's Disease, aging
- Cancer - it is estimated that about 15–20% of all cancer cases are preceded by chronic inflammation, including lung, colon and pancreatic cancers

REVIEW ARTICLE
Front. Aging Neurosci., 09 October 2018 | https://doi.org/10.3389/fnagi.2018.00312

Check for updates

Inflammation: Bridging Age, Menopause and APOEε4 Genotype to Alzheimer’s Disease

Aarti Mishra[1,2] and Roberta D. Brinton[2,3,4*]

[1]Titus Family Department of Clinical Pharmacy, School of Pharmacy, University of Southern California, Los Angeles, CA, United States
[2]Center for Innovation in Brain Science, University of Arizona, Tucson, AZ, United States
[3]Department of Pharmacology, College of Medicine, University of Arizona, Tucson, AZ, United States
[4]Department of Neurology, College of Medicine, University of Arizona, Tucson, AZ, United States

MENU nature International journal of science

NEWS AND VIEWS · 16 MAY 2018

Brain inflammatory cascade controlled by gut-derived molecules

Metabolite molecules produced by the gut’s microbes activate immune cells in the brain called microglia, which signal to astrocyte cells to mediate responses to inflammation in the central nervous system.

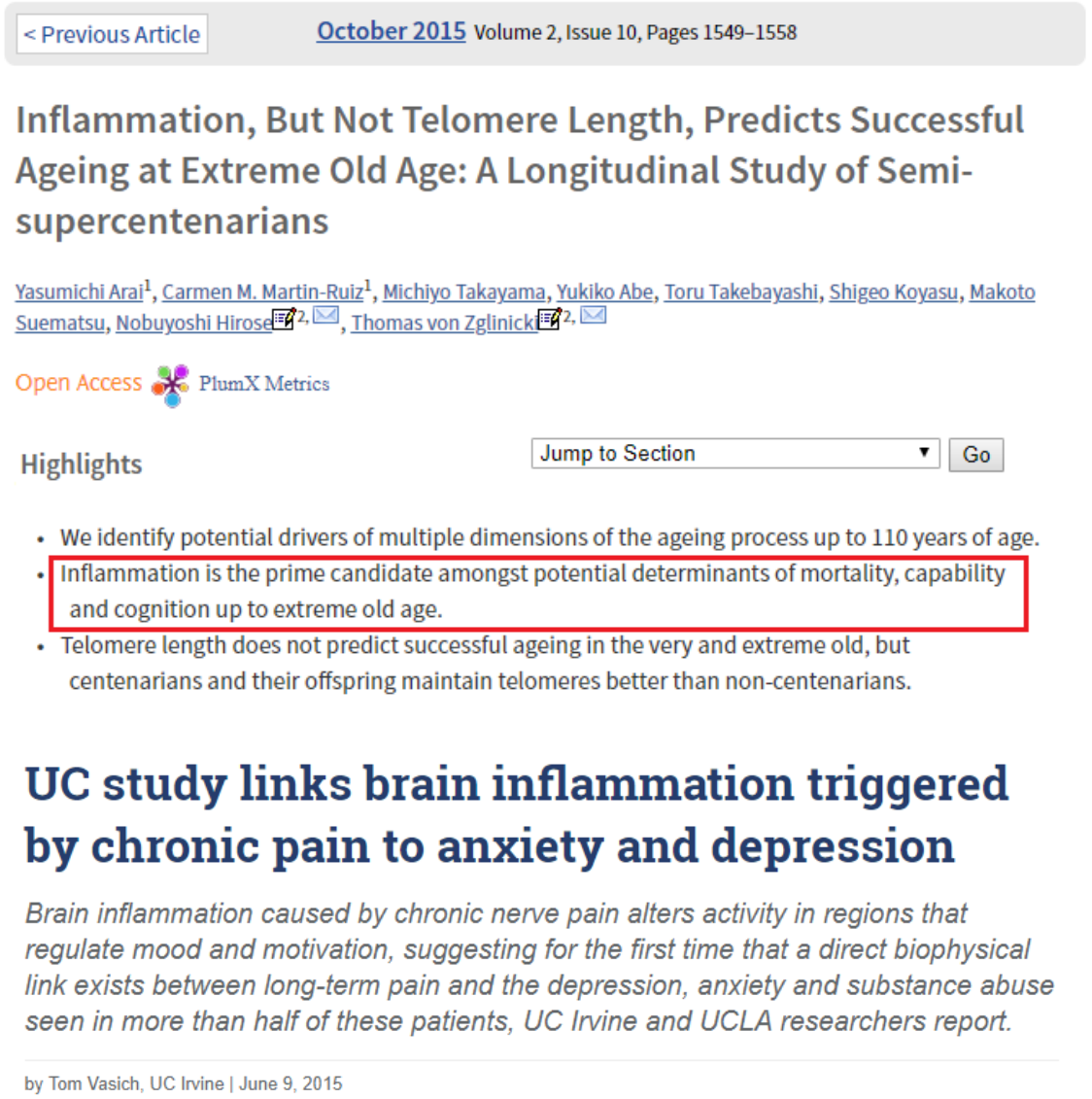
Hartmut Wekerle

Inflammation

Inflammation is a complex defense mechanism against biological and chemical insults

Although beneficial, persistent inflammation can cause cellular damage resulting in many diseases including:

- Obesity, diabetes, Inflammatory bowel disease
- Schizophrenia, anxiety, depression
- Parkinson's Disease, Alzheimer's Disease, aging
- Cancer - it is estimated that about 15–20% of all cancer cases are preceded by chronic inflammation, including lung, colon and pancreatic cancers



< Previous Article October 2015 Volume 2, Issue 10, Pages 1549–1558

Inflammation, But Not Telomere Length, Predicts Successful Ageing at Extreme Old Age: A Longitudinal Study of Semi-supercentenarians

Yasumichi Arai[1], Carmen M. Martin-Ruiz[1], Michiyo Takayama, Yukiko Abe, Toru Takebayashi, Shigeo Koyasu, Makoto Suematsu, Nobuyoshi Hirose[2], Thomas von Zglinicki[2]

Open Access PlumX Metrics

Highlights Jump to Section Go

- We identify potential drivers of multiple dimensions of the ageing process up to 110 years of age.
- Inflammation is the prime candidate amongst potential determinants of mortality, capability and cognition up to extreme old age.
- Telomere length does not predict successful ageing in the very and extreme old, but centenarians and their offspring maintain telomeres better than non-centenarians.

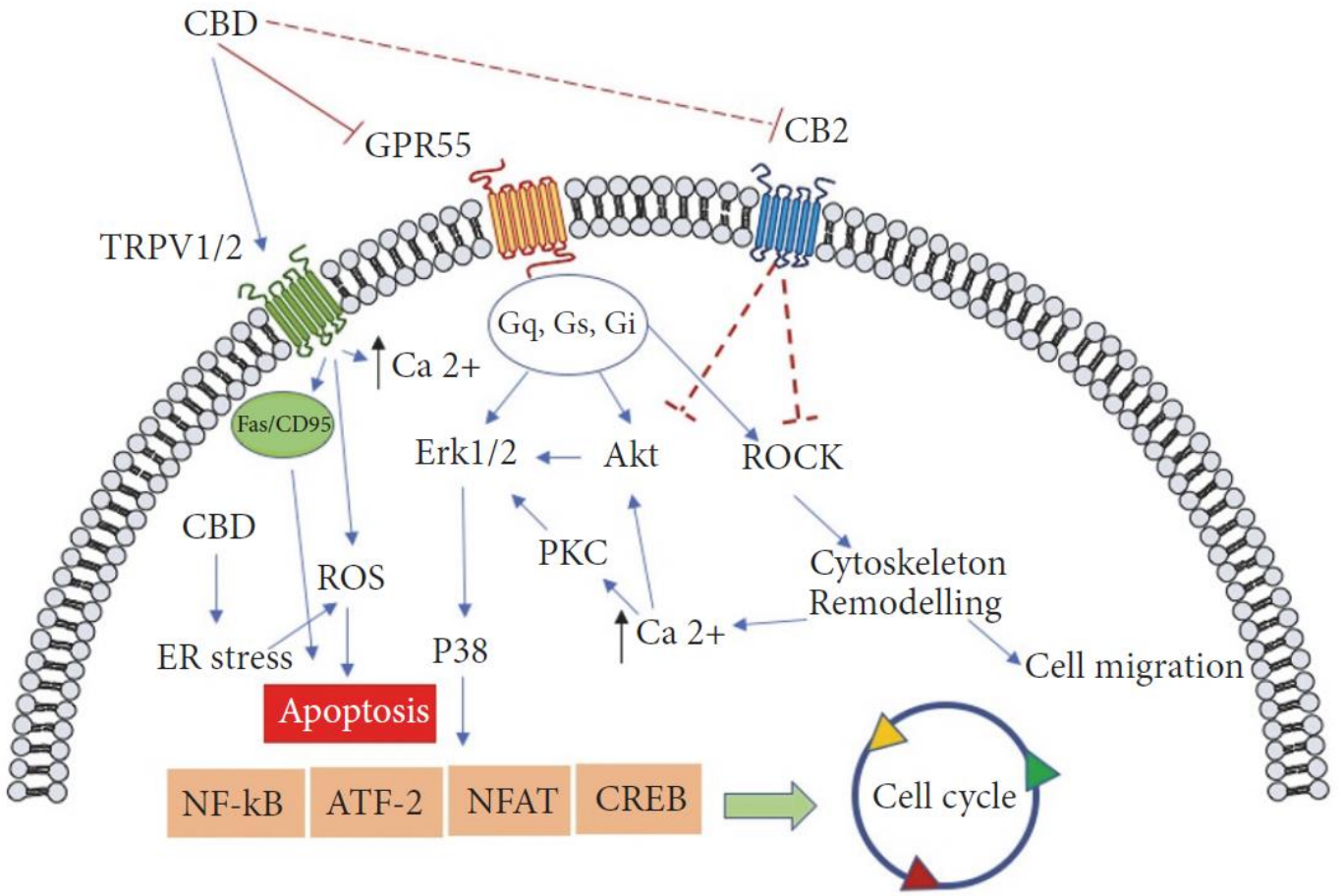
UC study links brain inflammation triggered by chronic pain to anxiety and depression

Brain inflammation caused by chronic nerve pain alters activity in regions that regulate mood and motivation, suggesting for the first time that a direct biophysical link exists between long-term pain and the depression, anxiety and substance abuse seen in more than half of these patients, UC Irvine and UCLA researchers report.

by Tom Vasich, UC Irvine | June 9, 2015

CBD anticancer effects

- **CBD anticancer effects mediated via TRPV1/2, GPR55 and CB2 receptors** > endoplasmic reticular stress, inhibition of the activation of ERK pathway, blocking of ROCK (antimigratory effect)



Pellati et al., 2018

Molecular Targets of Cannabidiol in Neurological Disorders

- > 68 discrete molecular targets have been reported in the literature for CBD
- CBD is very unlikely to exert effects in neurological diseases through modulation of the endocannabinoid system
- Other molecular targets of CBD reported in the literature are unlikely to be of relevance owing to effects only being observed at supraphysiological concentrations

Disease or disease group	Most plausible molecular targets of CBD
Epilepsy	VDAC1, CaV3.x, 5-HT_{1A}, GlyR, GPR55, adenosine modulation (ENT1)
Movement disorders	CaV3.x, 5-HT_{1A}, VDAC1
Neurodegenerative diseases	VDAC1, FABP, GPR55, NRF2, ENT1
Pain	TRPV1, TRPA1, TRPM8
Psychosis and anxiety	5-HT_{1A}, adenosine modulation (ENT1)
Addiction	CYP2D6, opioid receptors, ABCG2

VDAC1 = voltage-dependent anion channel 1; 5-HT = serotonin; GlyR = glycine receptor; GPR55 = G protein-coupled receptor 55; ENT1 = equilibrative nucleoside transporter 1; FABP = fatty acid binding protein; NRF2 = Nuclear factor erythroid 2-related factor 2; TRPV1 = transient receptor potential vanilloid-type 1; TRPA1 = transient receptor potential ankyrin type 1; TRPM8 = transient receptor potential subfamily M; CYP = cytochrome P

Ibeas Bih et al., 2015

CBD modulates THC effects

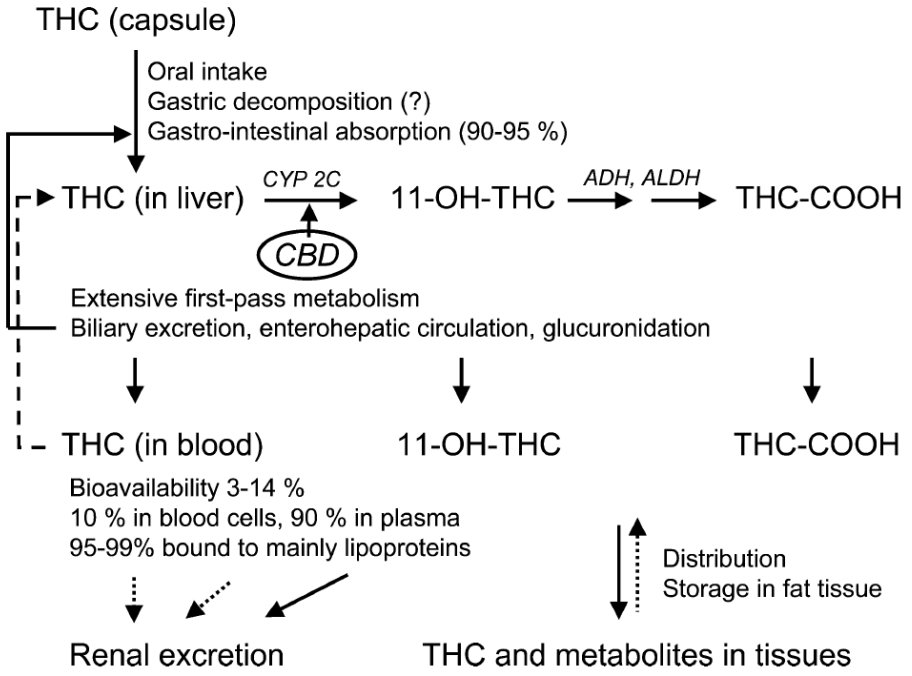
Pharmacokinetic modulation:

- Reduces the metabolites (11-OH-THC) of THC
- increases the level of THC (inhibition of enzymes by the CBD)
- reduces the peak induced by THC (delays the THC Tmax)
- prolongs the overall effect of THC

Guy et al., 2003, Nadulski et al., 2005

CBD modulates the effects of THC:

- anxiolytic effect
- antipsychotic effect
- counteracts tachycardia

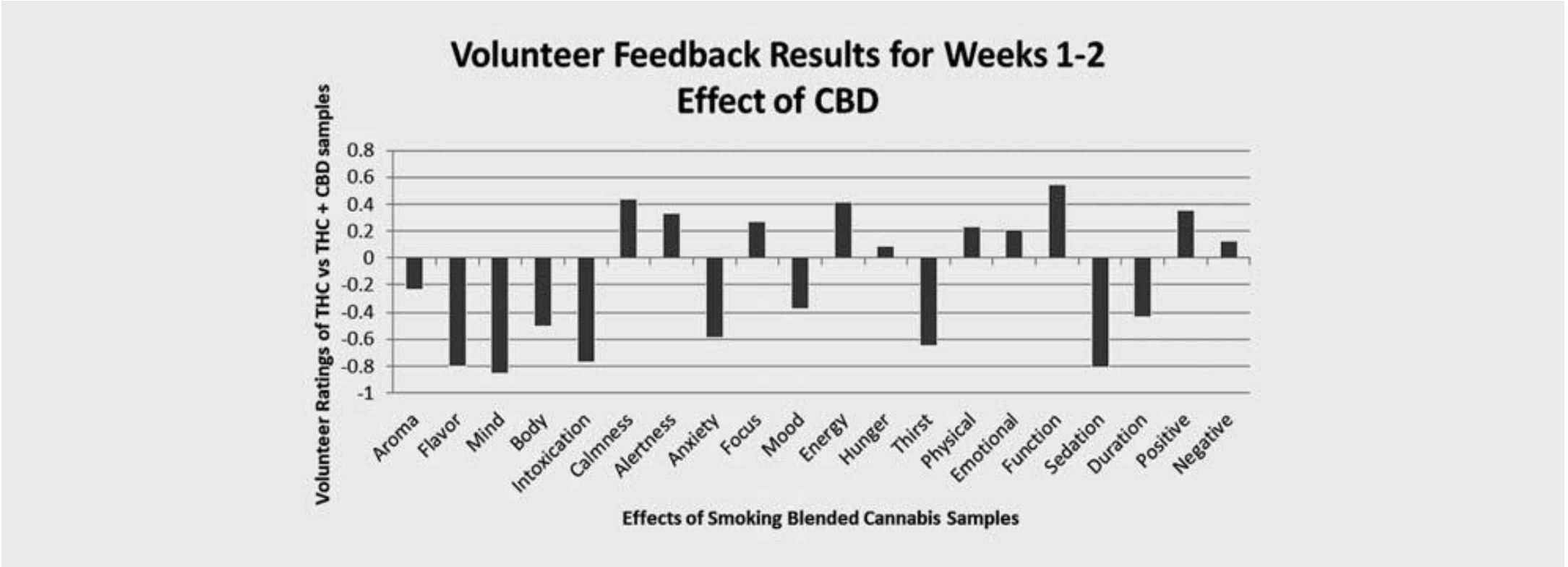


THC vs THC + CBD (*Lewis et al., 2017*)

With CBD:

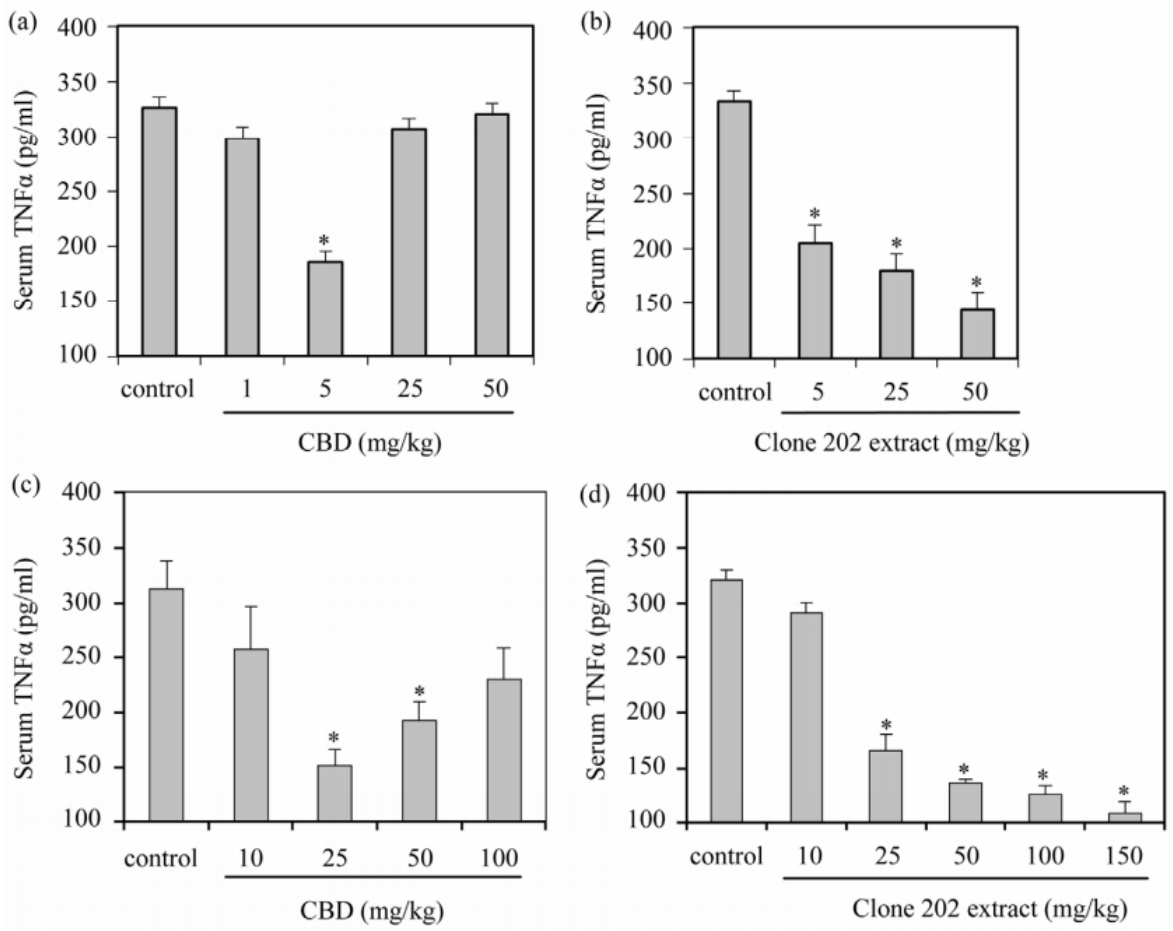
- decrease in “mind high”, “body high”, intoxication, sedation, and anxiety

+ increase in calmness, alertness, focus, energy, and ability to function



CBD vs. CBD-Rich Cannabis Extracts

- Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using *Cannabis* Extract Enriched in Cannabidiol
- CBD vs. CBD extract (CBD 17.9%, Δ9-THC 1.1%, CBC 1.1%, CBG 0.2%)
- „CBD in a standardized *Cannabis sativa* extract is more potent or efficacious than pure CBD“



Gallily et al. 2015

CBD vs. CBD-Rich Cannabis Extracts

CBD-Rich Cannabis Extracts vs. Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis

- **Higher** number of patients reporting improvement after using CBD-rich Cannabis extracts (318/447, **71%**) than those treated with purified CBD (81/223, **36%**)
- The average dose **4 x lower** CBD extracts compared to pure CBD
- CBD extracts **4 x "more potent"** than pure CBD

TABLE 2 | Efficacy of treatments in the reduction of convulsive seizures (heterogeneous population).

Treatment references	Patients	Reported improvement	>50%	>70%	Daily dose (weighted average) (mg/kg/day)
Total reports	**670**	**399/622**	**216/553**	**83/430**	**(2–50 mg/kg)**
Mean	**100%**	**64%**	**39%**	**19%**	**17.7 mg/kg**
CBD pure (6)	137	37%	37%	22%	22.9 mg/kg
CBD pure (7)	7	86%	71%	57%	22 mg/kg
CBD pure (8)	13	85%	70%	46%	24.6 mg/kg
CBD pure (9)	18	72%	50%	22%	37.7 mg/kg
CBD pure (10)	48	NR	42%	NR	28.2 mg/kg
CBD-rich extract (11)	19	84%	74%	42%	7.0 mg/kg
CBD-rich extract (12)	117	85%	NR	NR	4.3 mg/kg
CBD-rich extract (28)	75	57%	33%	NR	NR
CBD-rich extract (13)	74	89%	34%	18%	<10 mg/kg
CBD-rich extract (14)	43	83%	67%	42%	3.2 mg/kg
CBD-rich extract (15)	119	49%	24%	NR	NR

Endpoints: any improvement reported, improvement >50% ("clinical responder") and >70%, and average dose reported.

Pamplona et al., 2018

CBD vs. CBD-Rich Cannabis Extracts

CBD-Rich Cannabis Extracts vs. Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis

- **Higher** number of patients reporting improvement after using CBD-rich Cannabis extracts (318/447, **71%**) than those treated with purified CBD (81/223, **36%**)
- The average dose **4 x lower** CBD extracts compared to pure CBD
- CBD extracts **4 x "more potent"** than pure CBD
- CBD extracts tend to show **less adverse events**

TABLE 4 | Negative secondary effects of treatment with CBD-rich *Cannabis* extracts and purified CBD described as secondary endpoints in the clinical studies.

Treatment references	*n*	Mild AE	Serious AE	Total AE
Total reports	**663**	**285/663**	**64/487**	**326/663**
Mean	**100%**	**43%**	**13%**	**49%**
CBD pure (6)	137	79%	30%	128/137
CBD pure (9)	18	67%	0%	12/18
CBD pure (8)	13	77%	NR	10/13
CBD pure (10)	48	58%	NR	28/48
CBD-rich extract (11)	19	37%	0%	7/19
CBD-rich extract (12)	117	30%	0%	35/117
CBD-rich extract (28)	75	44%	13%	33/75
CBD-rich extract (13)	74	46%	18%	34/74
CBD-rich extract (14)	43	37%	0%	16/43
CBD-rich extract (15)	119	19%	NR	23/119

**Reporting adverse events in a study population does not necessarily mean that it is related to treatment. NR, not reported.*

Overview of CBD pharmacological effects *Pisanti eta Ia., 2017*

Disease	Effects	Refs
Alzheimer's disease	Antinflammatory, antioxidant, antiapoptotic in *in vitro* and *in vivo* models of Aβ-evoked neuroinflammatory and neurodegenerative responses.	Hayakawa et al. (2007), Esposito et al. (2006a), Esposito et al. (2006b), Martín-Moreno et al. (2011), Scuderi et al. (2014), Cheng et al. (2014)
Parkinson's disease	Attenuation of the dopaminergic impairment *in vivo*; neuroprotection; improvement of psychiatric rating and reduction of agitation, nightmare and aggressive behaviour in patients.	Lastres-Becker et al. (2005), Zuardi et al. (2009), Chagas, Eckeli, et al. (2014)
Multiple sclerosis	Improved signs of EAE in mice, antinflammatory and immunomodulatory properties.	Buccellato et al. (2011), Kozela et al. (2011, 2015), Mecha et al. (2013), Giacoppo et al. (2015)
Epilepsy	Anticonvulsant *in vitro* and *in vivo*; reduced seizures frequency in children and adults with treatment-resistant epilepsy.	Pertwee (2008), Devinsky et al. (2016)
Huntington's disease	Neuroprotective and antioxidant in mice transgenic models; no significant clinically important differences in patients.	Iuvone et al. (2009), Sagredo et al. (2011), Consroe et al. (1991)
Hypoxia-ischemia injury	Short term neuroprotective effects; inhibition of excitotoxicity, oxidative stress and inflammation *in vitro* and in rodent models.	Pazos et al. (2012, 2013), Hayakawa et al. (2007, 2009), Valdepeñas et al. (2011)
Pain	Analgesic effect in patients with neuropathic pain resistant to other treatments.	Petzke et al. (2016), Boychuk et al. (2015)
	Attenuation of the behavioural and glial changes in animal models of schizophrenia; anti-psychotic properties on ketamine-induced symptoms.	Crippa et al. (2015), Gomes et al. (2015), Zuardi et al. (2006, 2012)
Anxiety	Reduction of muscular tension, restlessness, fatigue, problems in concentration, improvement of social interactions in rodent models of anxiety and stress; reduced social anxiety in patients.	Lemos et al. (2010), Almeida et al. (2013), Moreira et al. (2006), de Mello Schier et al. (2014), Bergamaschi et al. (2011), Marinho et al. (2015)
Depression	Anti-depressant effect in genetic rodent model of depression.	El-alfy et al. (2010), Hsiao et al. (2012), Shoval et al. (2016)
Cancer	Antiproliferative and anti-invasive actions in a large range of cancer types; induction of autophagy-mediated cancer cell death; chemopreventive effects.	Ligresti et al. (2006), McAllister et al. (2011), Shrivastava et al. (2011), Pisanti et al. (2013), Rocha et al. (2014), Ramer et al. (2014), Scott et al. (2014)
Nausea	Suppression of nausea and conditioned gaping in rats	Parker et al. (2002), Rock et al. (2008)
Inflammatory diseases	Antinflammatory properties in several in vitro and in vivo models; inhibition of inflammatory cytokines and pathways.	Ribeiro et al. (2012, 2015), Kozela et al. (2010, 2011), Mecha et al. (2012, 2013)
Rheumatoid arthritis	Inhibition of TNF-α in an animal model	Malfait et al. (2000)
Infection	Activity against methicillin-resistant *Staphylococcus aureus*	Appendino et al. (2008)
Inflammatory bowel and Chron's diseases	Inhibition of macrophage recruitment and TNF-α secretion *in vivo* and *ex vivo*; reduction in disease activity index in Chron's patients.	Sacerdote et al. (2005), De Filippis et al. (2011), Naftali et al. (2011)
Cardiovascular diseases	Reduced infarct size through anti-oxidant and anti-inflammatory properties *in vitro* and *in vivo*.	Durst et al. (2007), Booz (2011), Stanley et al. (2013)
Diabetic complications	Attenuation of fibrosis and myocardial dysfunction	Weiss et al. (2006, 2008), Rajesh et al. (2010), Kozela et al. (2010)

A Cross-Sectional Study of Cannabidiol Users *Corroon et al., 2018*

Online survey (anonymous questionnaire) of individuals currently using CBD (n = 2409)

Number of medical conditions for which respondents reported using CBD, by medical condition (n = 3963)

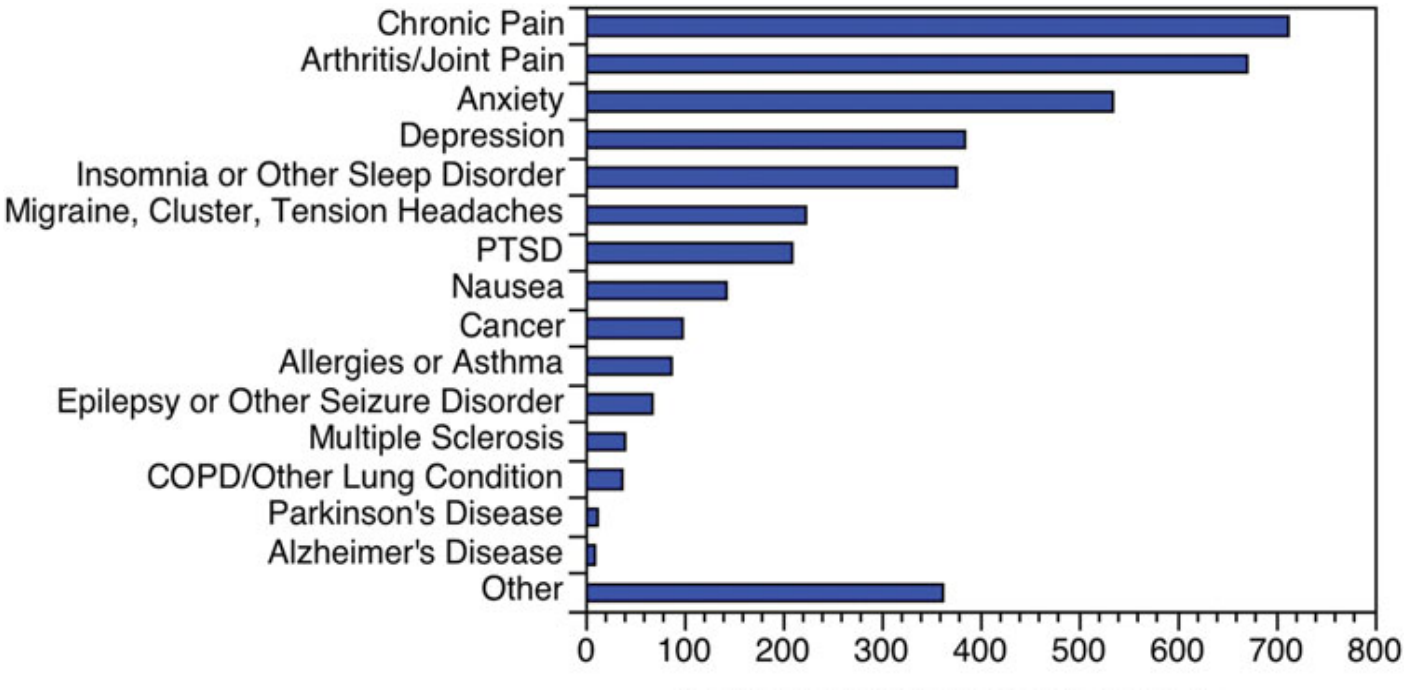


Table 1. Sociodemographic and Other Characteristics of Survey Respondents (*n* = 2409)

	n (%)
Gender	
Male	1013 (47.40)
Female	1087 (50.87)
Decline to state	37 (1.73)
Missing	272
Age (years)	
≤24	138 (6.33)
25–34	292 (13.40)
35–44	400 (18.36)
45–54	404 (18.54)
55–64	532 (24.41)
65–74	339 (15.56)
≥75	74 (3.40)
Missing	230
Education	
Primary/middle school	22 (1.01)
High school/GED	503 (23.13)
College	1138 (52.32)
Postgraduate	411 (18.90)
Other	101 (4.64)
Missing	234
Geography	
United States	1987 (91.23)
Canada/Mexico	103 (4.73)
Other	88 (4.04)
Missing	231
Geography—U.S. states (top 5)	
California	412 (21.90)
Texas	93 (4.94)
Oregon	83 (4.41)
Florida	79 (4.20)
Colorado	76 (4.04)
Missing	528
Cannabis use	
Regular	1189 (55.17)
Nonregular	966 (44.83)
Missing	254
CBD use	
General health and well-being	926 (38.44)
Medical condition	1483 (61.56)
Missing	0

A Cross-Sectional Study of Cannabidiol Users *Corroon et al., 2018*

Online survey (anonymous questionnaire) of individuals currently using CBD (n = 2409)

Number of medical conditions for which respondents report CBD treating ‘‘Very well by itself’’ or ‘‘Moderately well by itself’’ by medical condition (n = 2557)

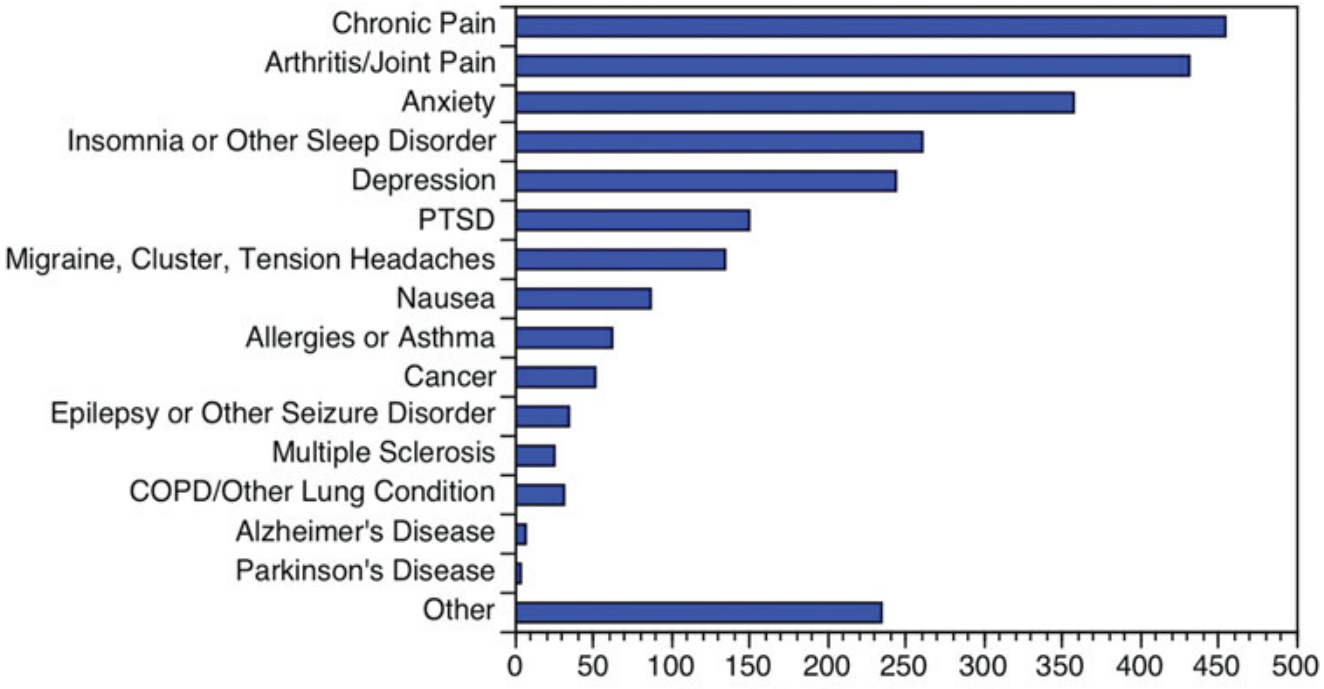


Table 1. Sociodemographic and Other Characteristics of Survey Respondents ($n = 2409$)

	n (%)
Gender	
Male	1013 (47.40)
Female	1087 (50.87)
Decline to state	37 (1.73)
Missing	272
Age (years)	
≤24	138 (6.33)
25–34	292 (13.40)
35–44	400 (18.36)
45–54	404 (18.54)
55–64	532 (24.41)
65–74	339 (15.56)
≥75	74 (3.40)
Missing	230
Education	
Primary/middle school	22 (1.01)
High school/GED	503 (23.13)
College	1138 (52.32)
Postgraduate	411 (18.90)
Other	101 (4.64)
Missing	234
Geography	
United States	1987 (91.23)
Canada/Mexico	103 (4.73)
Other	88 (4.04)
Missing	231
Geography—U.S. states (top 5)	
California	412 (21.90)
Texas	93 (4.94)
Oregon	83 (4.41)
Florida	79 (4.20)
Colorado	76 (4.04)
Missing	528
Cannabis use	
Regular	1189 (55.17)
Nonregular	966 (44.83)
Missing	254
CBD use	
General health and well-being	926 (38.44)
Medical condition	1483 (61.56)
Missing	0

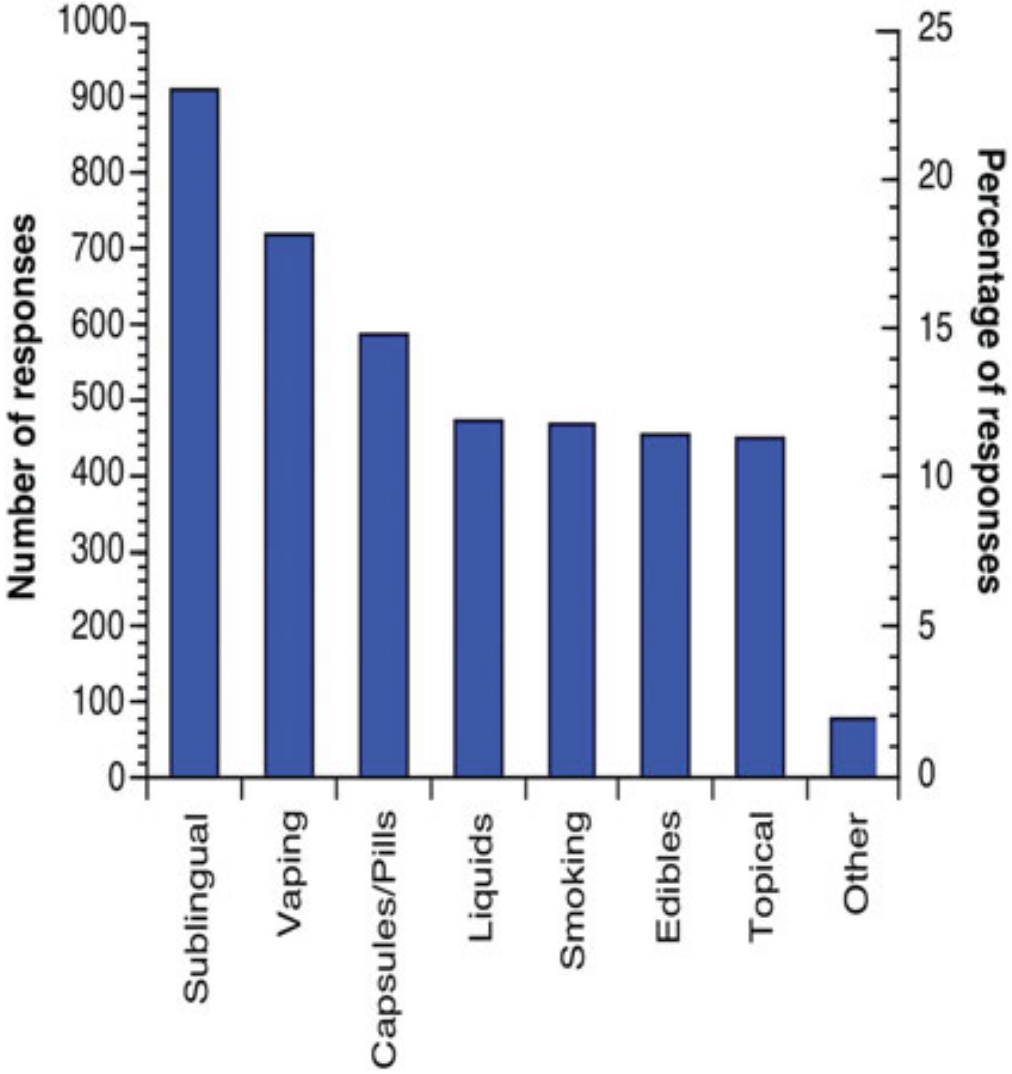
A Cross-Sectional Study of Cannabidiol Users *Corroon et al., 2018*

Online survey (anonymous questionnaire) of individuals currently using CBD (n = 2409)

Number and percentage of methods of administering CBD (n = 4135)

Most common adverse effects reported by survey respondents (n = 742)

- Dry mouth 268 (11.12%)
- Euphoria 155 (6.43%)
- Hunger 153 (6.35%)
- Other 57 (2.37%)
- Red eyes 66 (2.74%)
- Sleepy/groggy 43 (1.78%)



Cannabidiol in Anxiety and Sleep: A Large Case Series

- 72 adults primary concerns of anxiety (n = 47) or poor sleep (n = 25)
- Dose CBD 25 mg/d – 175 mg/d
- Anxiety scores decreased within the first month in 57 patients(79.2%) and remained decreased during the study duration
- Sleep scores improved within the first month in 48 patients (66.7%) but fluctuated over time
- CBD was well tolerated, with few patients reporting side effects (fatigue (2), mild sedation (3), dry eyes (1))

Table 1. Descriptive statistics for anxiety and sleep scores among adults using cannabidiol treatment

Parameter	HAM-A, mean (SD)	PSQI, mean (SD)
Anxiety (n = 47)		
Baseline	23.87 (9.87)	10.98 (3.43)
1-month follow-up	18.02 (7.56)	8.88 (3.68)
2-month follow-up	16.35 (8.80)	8.59 (2.91)
3-month follow-up	16.36 (9.80)	9.25 (2.46)
Sleep disorder (n = 25)		
Baseline	22.18 (7.55)	13.08 (3.03)
1-month follow-up	17.82 (9.72)	10.64 (3.89)
2-month follow-up	17.36 (10.91)	9.39 (3.81)
3-month follow-up	13.78 (7.86)	9.33 (4.63)

HAM-A = Hamilton Anxiety Rating Scale; PSQI = Pittsburg Sleep Quality Index; SD = standard deviation.

Shannon et al., 2019

CBD safety and side effects

CBD safety

- CBD is well tolerated and safe in humans at high doses and with chronic use
- Some *in vitro* and *in vivo* studies showed potential drug metabolism interactions (CYP450), cytotoxicity, and decreased receptor activity
- To be determined - CBD effects on hormones
- More clinical trials with a greater number of participants and longer chronic CBD administration

CBD side effects

CBD - usually there are no side effects

Studies only with pure CBD, even less with the extract

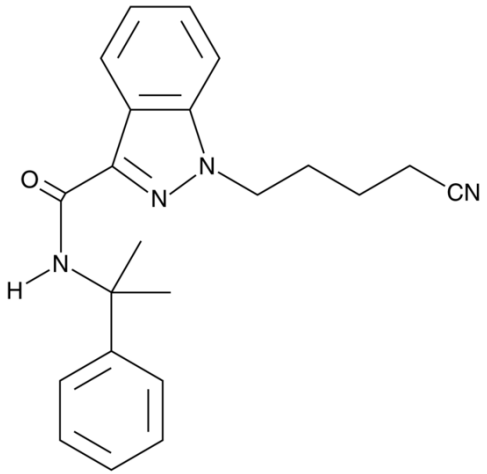
At higher doses (up to 600 mg / day), the most common side effects (in less than 10% of patients):

- drowsiness
- indigestion
- fatigue
- decreased appetite

Iffland, K., & Grotenhermen, 2017

52 people intoxicated by the fake CBD oil

- The CDC report found that over half of the 52 possible cases were positive for a synthetic compound called **4-CCB** or reported using a product called **Yolo CBD Oil**, whose samples contained the synthetic instead of the authentic CBD
- **4-CCB** (4-cyano CUMYL-BUTINACA)



52 people sickened by fake CBD oil in Utah, that is not good news!

Posted on May 30, 2018 at 10:42 pm.

"In a report released Thursday, the Centers for Disease Control and Prevention found that synthetic products falsely labeled as cannabidiol, or CBD, sickened as many as 52 people from October through January."

The CDC report this week found that more than half of the 52 possible cases either tested positive for a synthetic compound called 4-CCB or reporting using a product called Yolo CBD Oil, samples of which contained the synthetic instead of authentic CBD. Efforts to determine what company manufactures Yolo CBD Oil were not successful."

CBD “oils” - EU market

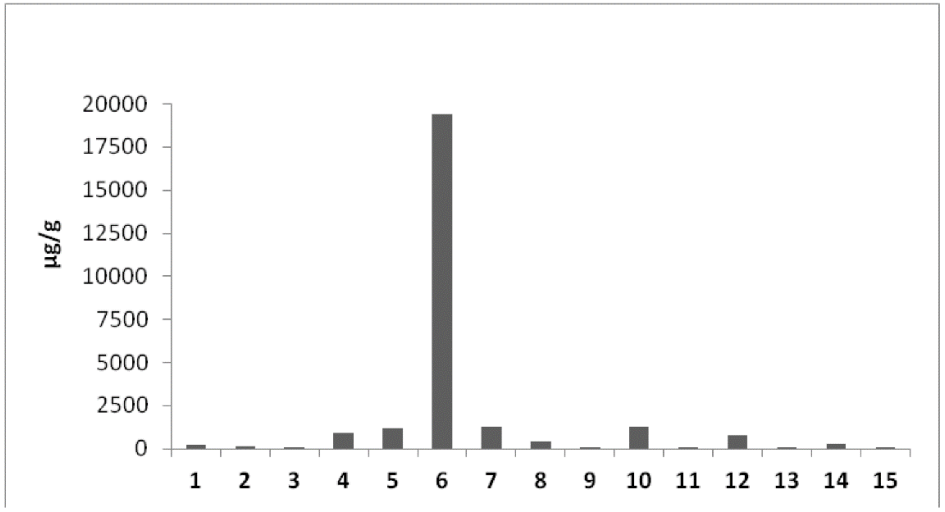
CBD content:

- 9 out of the 14 samples studied had concentrations that differed notably from the label (*2 higher, 2 notably lower*)
- 5 preserved CBD within optimal limits (variation less than 10%)

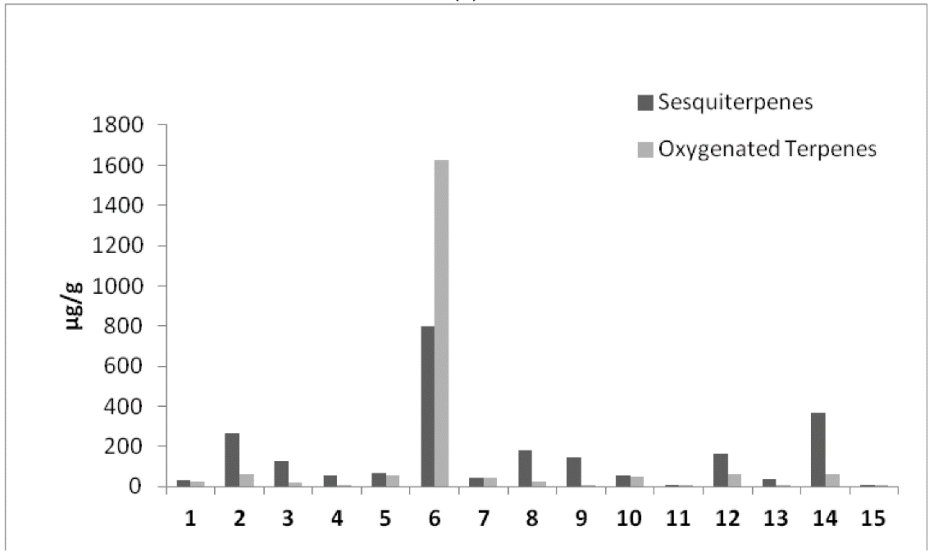
Terpenes:

- sample 6 contained high amount of terpenes (*α-Pinene, β-myrcene limonene*) compared with all other samples (but also had 0.35% THC)

Pavlović et al., 2018



(a)



(b)

Cannabigerol (CBG)

Isolated 1964 (*Gaoni & Mechoulam, 1964*)

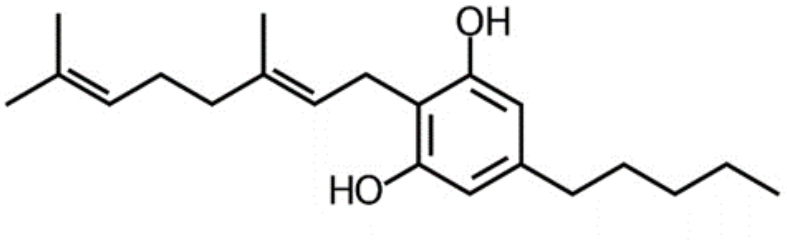
Non-intoxicating (*Grunfeld and Edery, 1969; Mechoulam et al., 1970*)

CB2 - partial agonist (*Navarro et al., 2018*)

CB1 -???

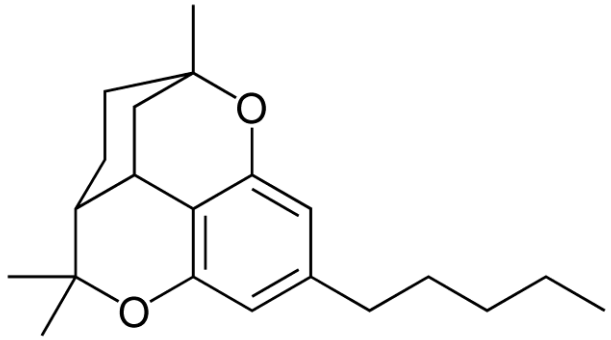
Agonist (TRPV1-4, α2-adrenoceptor), Antagonist (TRPV8, TRPM8), inhibitor of AEA cell uptake (*De Petrocellis et al., 2011*)

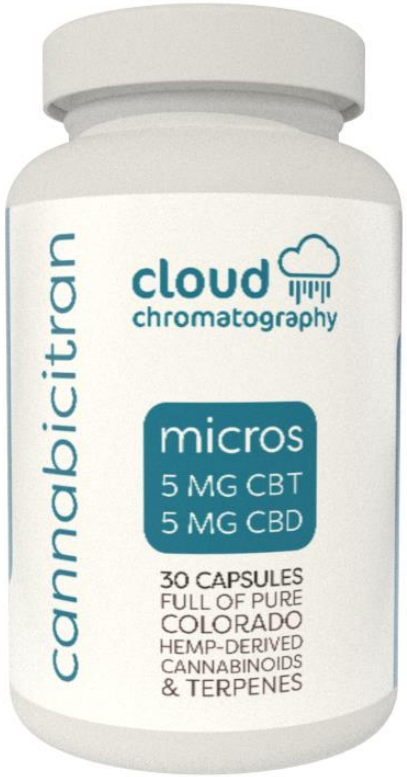
- Analgesic (*Cascio et al., 2010*)
- Anticancer (*Ligresti et al., 2006*)
- Anxiolytic (*Formukong et al., 1988*)
- Antidepressant (*Cascio eta l., 2010*)
- Antibiotic (*De Petrocellis et al., 2011*)



Cannabicitran (CBT)

- Isolated 1974 (*Bercht et al., 1974*)
- Found in the pollen of *Cannabis sativa* L. (*Ross et al., 2005*)
- It is not present in tobacco smoke (*Novotný et al., 1981*)
- Decreases intraocular pressure in rabbits (1 and 10 mg/kg, i.v.) (*ElSohly et al., 1984*)





The future of CBD?

- More data
- Listen to patients
- Quality assurance
- Testing
- Consumer products
- Laws and regulations