Medical Marijuana Research in Pennsylvania

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Penn State College of Medicine

17th June 2021
PA Psychological Association Annual Convention (PPA2021)

The speaker receives a sponsored research agreement from PA Options for Wellness – a PA-approved medical marijuana company

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OBJECTIVES

- **Compare and contrast medical marijuana programs in PA and the rest of the nation**
- **Explore barriers and concerns for medical marijuana/CBD use and research.**
- **Discuss marijuana versus hemp (THC versus CBD)**

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Historical Perspective - I

- ca 2900 BC – Chinese Emperor Fu Hsi: "Ma [cannabis] is a popular medicine with both yin and yang."
- 1500 BC – Written reference to cannabis in Chinese pharmacopeia
- 1621 – English mental health book (depression)
- 1745-1824 – Washington/Jefferson cultivated hemp
- 1850 – Officially in the US Pharmacopeia
  - Neuralgia - Tetanus
  - Alcoholism - Dysentery
  - Convulsive disorders - Insanity

www.medicalmarijuana.procon.org

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Historical Perspective - II

- 1906 – US Food and Drugs Act
- 1911-1927 – States begin prohibiting use of marijuana
- 1930s – "Reefer Madness" and Marijuana Tax Act (1937) although it was universally illegal at this point
- 1942 – Removed from the US Pharmacopeia
- 1964 – THC characterized
- 1968 – University of Mississippi designated as source
- 1970 – Controlled Substances Act declares "Marijuana is a drug with no accepted medical use"
- 1990 – Cannabinoid receptors discovered

www.medicalmarijuana.procon.org

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What are the Options

- **Legalize everything – including recreational marijuana (e.g., Washington, Colorado)**
- **Legalize medical "pot"**
- **Legalize medical extracts**
  - **Pennsylvania Act 16 (April 17, 2016)**
- **No legalization, but no prosecution of non-psychoactive molecules (e.g., CBD and the 2018 Farm Bill) – but the unintended consequences for delta-8-THC.**

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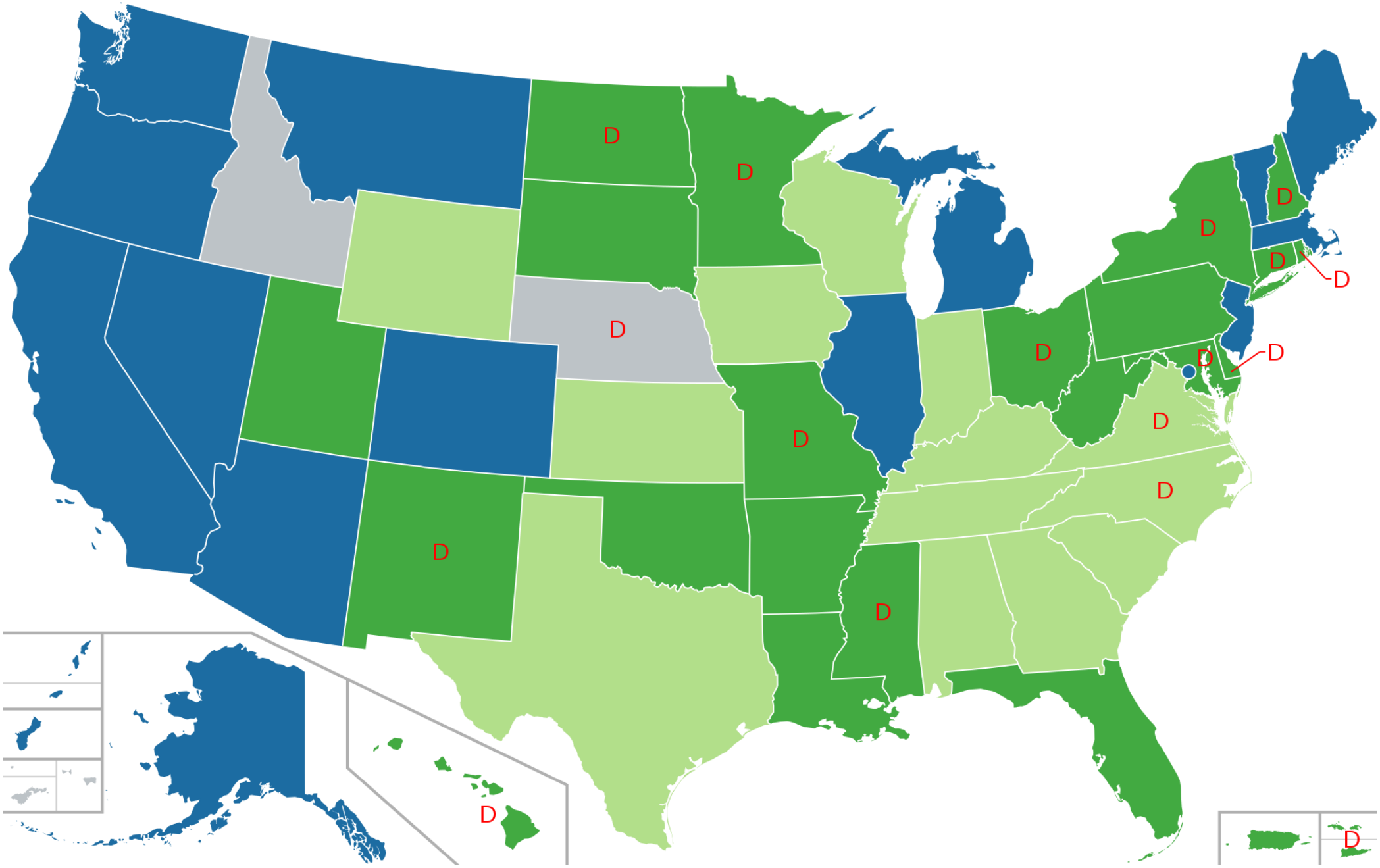
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Pennsylvania Act 16 – Medical Marijuana Act

- **Section 102 – The general assembly finds and declares as follows:**

1) Scientific evidence suggests that medical marijuana is one potential therapy that may mitigate suffering in some patients and also enhance the quality of life.

2) Carefully regulating the program which allows access to medical marijuana will enhance patient safety . . .

3) It is the intent of the General Assembly to:

- **i) Provide a program of access to medical marijuana. .**
- **ii) Provide a safe and effective method of delivery of medical marijuana to patients.**
- **iii) Promote high quality research . . .**

Act 16 – Approved Indications

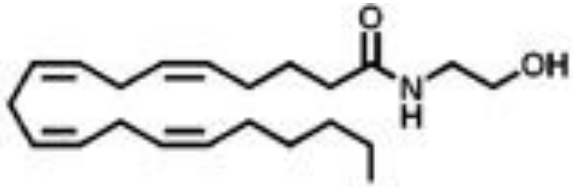
- Cancer
- HIV/AIDS
- Amyotrophic lateral sclerosis (ALS)
- Parkinson's disease
- Multiple sclerosis
- Spinal cord injury (with spasticity)
- Epilepsy
- Inflammatory bowel disease
- Neuropathies
- Huntington's disease
- Crohn's disease
- Post-traumatic stress disorder
- Intractable seizures
- Glaucoma
- Sickle cell anemia
- Intractable pain
- Autism

May 15th, 2018 – added Opioid Addiction; Spasticity; Neurodegeneration; and Terminal Illness

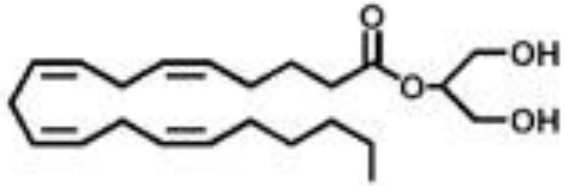
July 11, 2019 – added Anxiety; Tourette's Syndrome

Medical Marijuana: The Pharmacology of Medicinal Cannabinoids

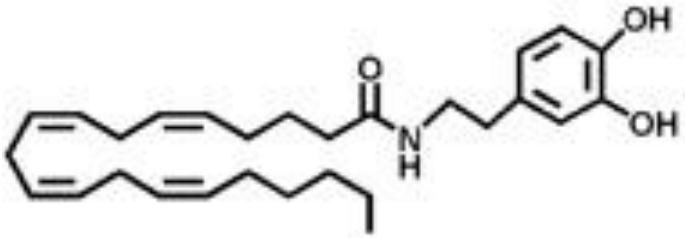
Medicinal Cannabinoids: Endocannabinoids



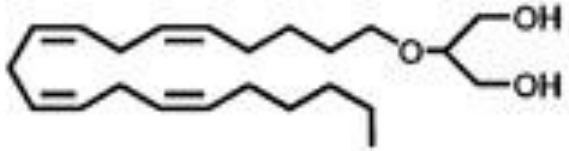
N-Arachidonoylethanolamine
(Anandamide, AEA)



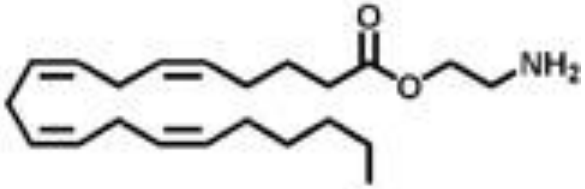
2-Arachidonoylglycerol
(2-AG)



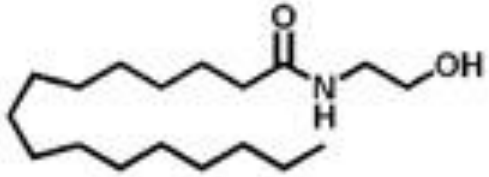
N-Arachidonoyldopamine
(NADA)



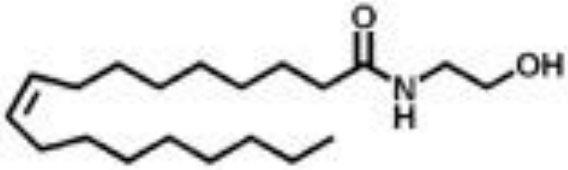
2-Arachidonoylglycerylether
(Noladin ether)



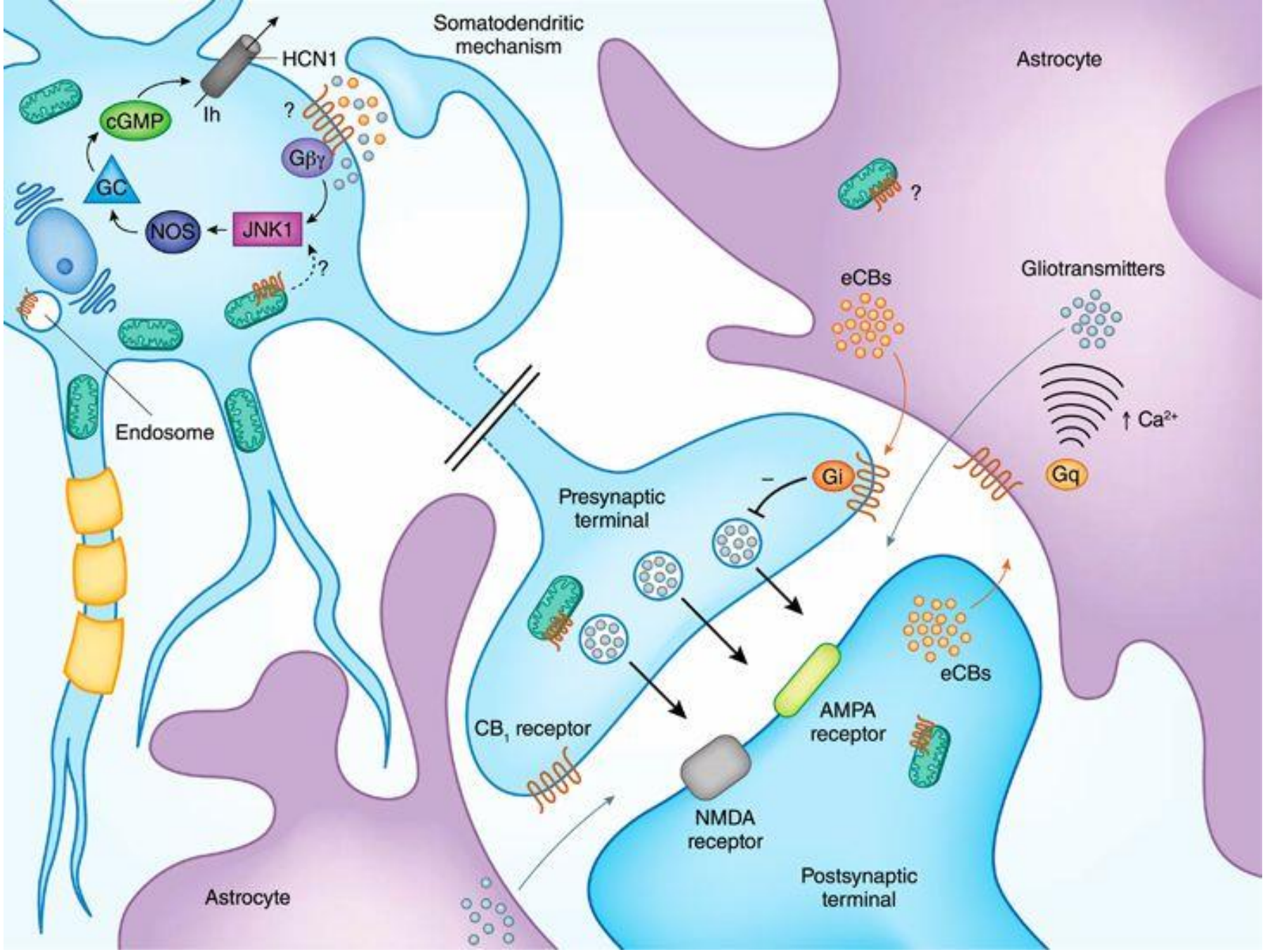
O-Arachidonoylethanolamine
(Virodhamine)



N-Palmitoylethanolamine
(PEA)

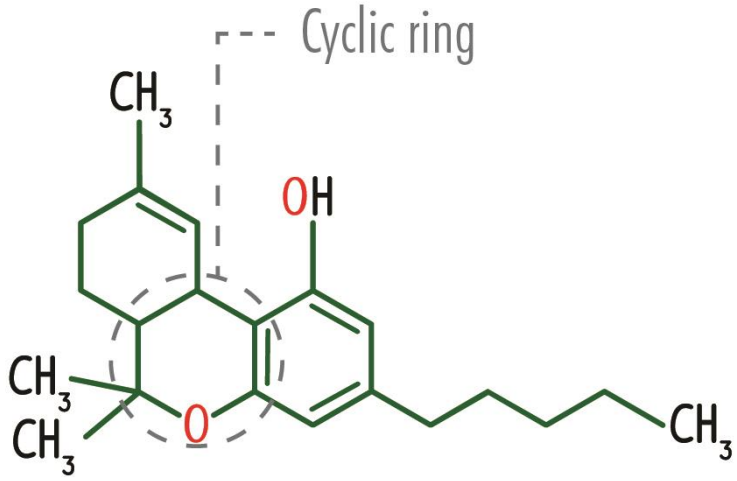


N-Oleoylethanolamine
(OEA)

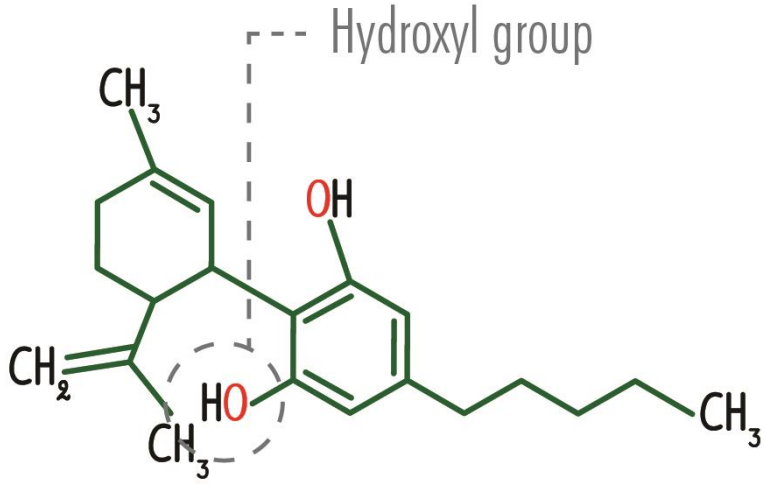


Busquets-Garcia et al. (2018) Neuropsychopharm Rev 43:4-20.

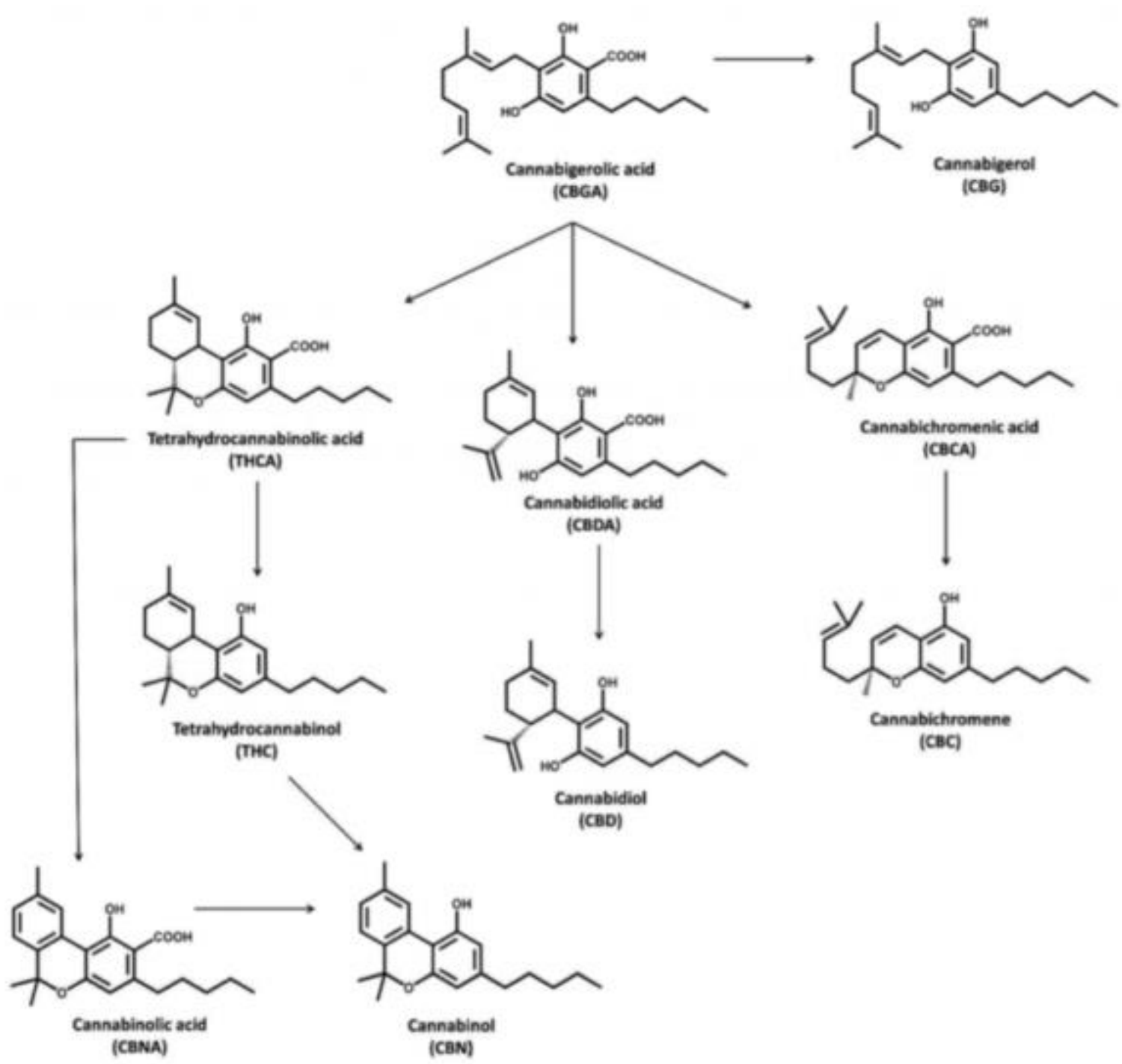
Phytocannabinoids: Medical Marijuana

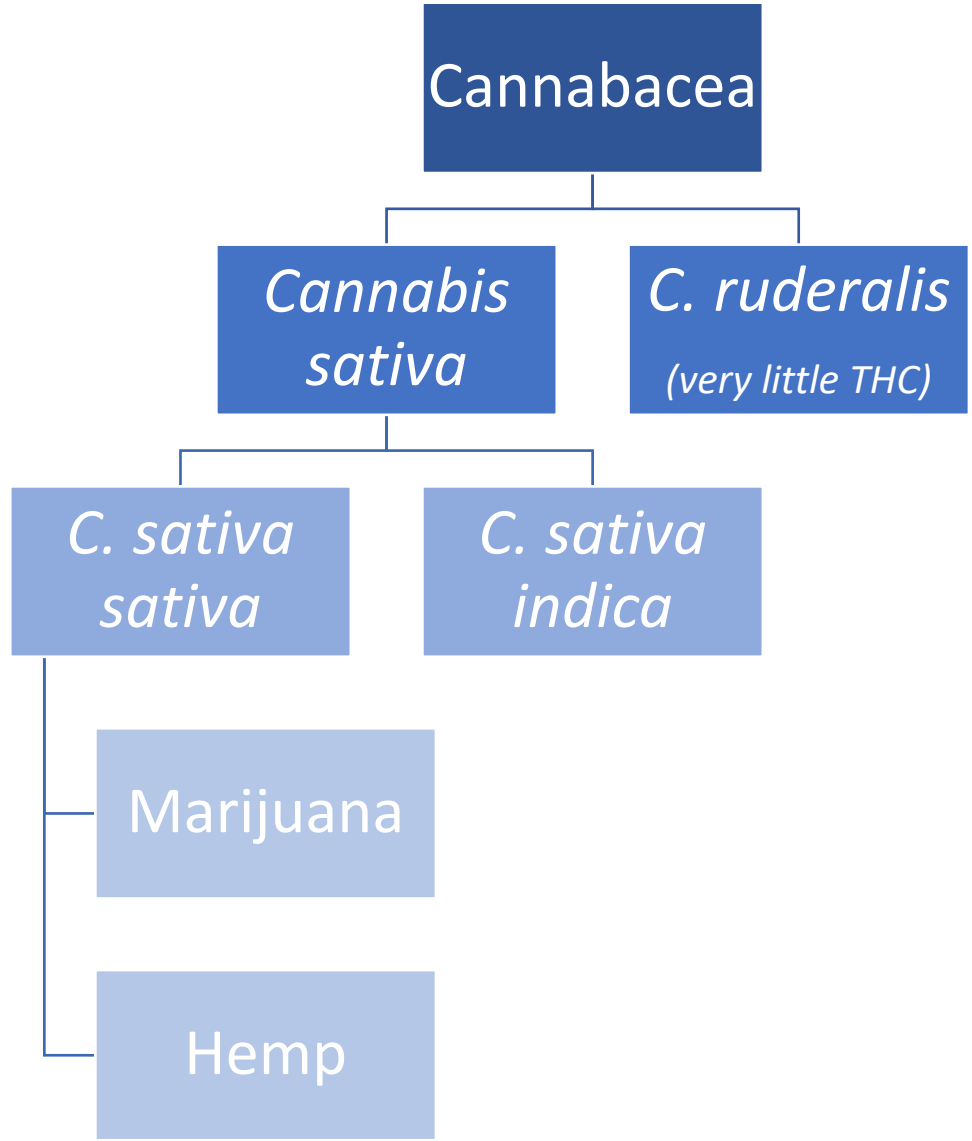


Tetrahydrocannabinol (THC)



Cannabidiol (CBD)

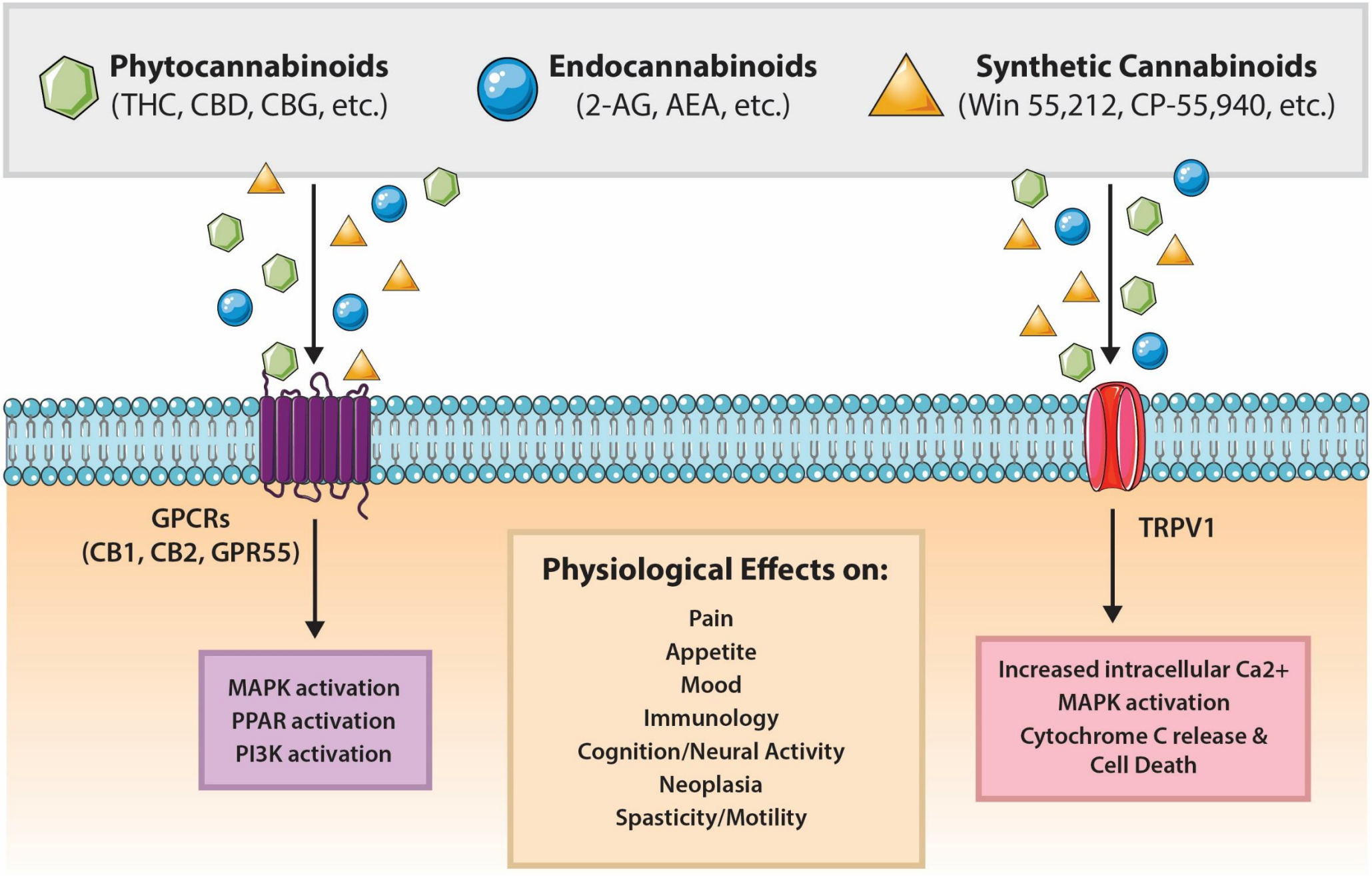

Cannabigerolic acid
(CBGA)
Cannabigerol
(CBG)
Tetrahydrocannabinolic acid
(THCA)
Cannabidiolic acid
(CBDA)
Cannabichromenic acid
(CBCA)
Tetrahydrocannabinol
(THC)
Cannabidiol
(CBD)
Cannabichromene
(CBC)
Cannabinolic acid
(CBNA)
Cannabinol
(CBN)


Cannabacea
Cannabis sativa
C. ruderalis
(very little THC)
C. sativa sativa
C. sativa indica
Marijuana
Hemp

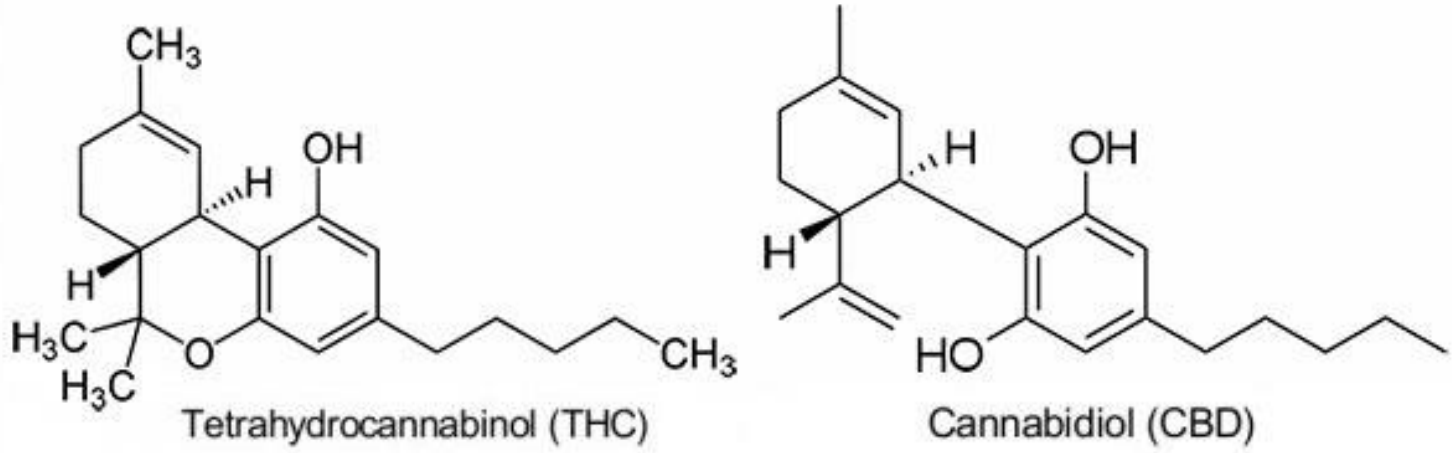
Strain	Category	CBD	THC	Conditions
Acapulco Gold	Sativa	0.1%	15-23%	Fatigue, stress, nausea, pain
Blue Dream	Hybrid	<1%	30%	Pain, cramps, inflammation, insomnia, mental fog, PTSD
Purple Kush	Indica	<1%	17-22%	Chronic pain, muscle spasms, insomnia
Sour Diesel	Sativa	<1%	20-22%	Fatigue, stress, acute pain, mental fog, anxiety, PTSD
Bubba Kush	Indica	<1%	14-25%	Insomnia, acute pain, nausea, low appetite, PTSD
Granddaddy Purple	Indica	<0.1%	17-23%	Low appetite, restless leg syndrome, insomnia
Afghan Kush	Indica	6%	16-21%	Acute pain, insomnia, low appetite
LA Confidential	Indica	0.3%	16-20%	Inflammation, pain, stress
Maui Waui	Sativa	0.55%	13-19%	Fatigue, depression
Golden Goat	Hybrid	1%	23%	Depression, anxiety, mental fog, low energy
Northern Lights	Indica	0.1%	16%	Pain, mood disorders, insomnia, low appetite
White Widow	Hybrid	<1%	12-20%	Low mood, mental fog, social anxiety
Super Silver Haze	Sativa	<0.1%	16%	Stress, anxiety, mental fog, low energy
Pineapple Express	Hybrid	<0.1%	23%	Mental fog, acute pain, social anxiety
Supernatural	Sativa	<1%	22%	Migraine, glaucoma, headaches, low moods

Cannabinoid Receptors

- **Four types of cannabinoid receptors (CB1, CB2, GPR-55 (CB3?), and TRPV1 (capsaicin receptor)**
- **7TM-GPCRs (CB1/2, GPR-55) and cation channel (TRPV1)**
- **CB1 is in brain and periphery and most abundant GPCR – responsible for psychoactive effects**
- **CB2 in periphery promising target for therapeutics**


Phytocannabinoids
(THC, CBD, CBG, etc.)
Endocannabinoids
(2-AG, AEA, etc.)
Synthetic Cannabinoids
(Win 55,212, CP-55,940, etc.)
GPCRs
(CB1, CB2, GPR55)
TRPV1
MAPK activation
PPAR activation
PI3K activation
Physiological Effects on:
Pain
Appetite
Mood
Immunology
Cognition/Neural Activity
Neoplasia
Spasticity/Motility
Increased intracellular Ca2+
MAPK activation
Cytochrome C release &
Cell Death

Medicinal Cannabinoids: Medical Marijuana



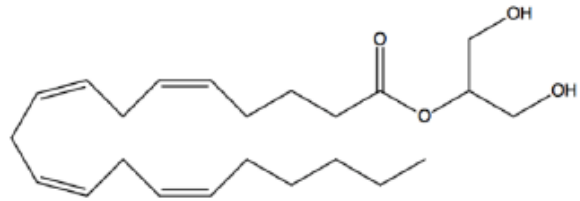
- **THC is a partial agonist**
- **CBD is controversial (weak antagonist, inverse agonist at CBs, and weak agonist at TRPV1), but clearly not psychoactive**

Legal Cannabinoid Drugs

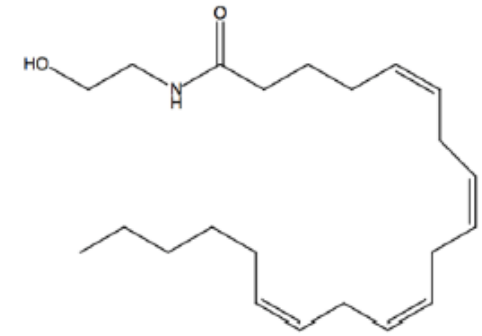
- **Marinol (dronabinol)**
  - **Appetite stimulant (HIV/AIDS; cancer chemotherapy)**
- **Syndros (liquid dronabinol)**
- **Cesamet (nabilone)**
  - **Structure similar to Δ9-THC**
  - **Antiemetic (treat nausea and vomiting)**
- **Sativex (equal parts Δ9-THC and CBD [plus other cannabinoids])**
  - **Treating spasticity in MS; approved in 16 countries outside US)**

Legal Cannabinoid Drugs

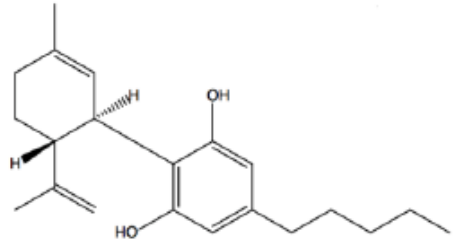
- **Acomplia (rimonabant)**
  - **Potent CB1 inverse agonist/antagonist (weak at CB2)**
  - **Appetite suppressant in Europe (withdrawn in 2009)**
- **Latest change occurred on June 25, 2018 when the FDA approved Epidiolex (cannabidiol)**
  - **Oral solution**
  - **Treatment of seizures associated with two rare and severe forms of childhood epilepsy - Lennox-Gastaut syndrome and Dravet syndrome**
- **CBD Oil (Over the Counter) (Farm Bill of 2018)**



2-Arachidonoylglycerol(2-AG)



Anandamide (AEA)



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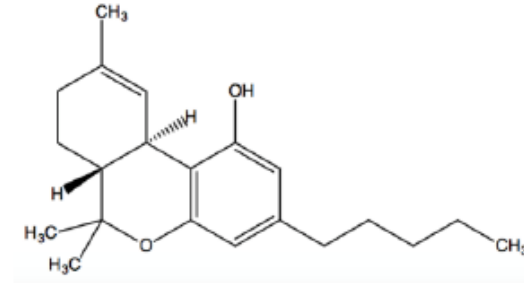
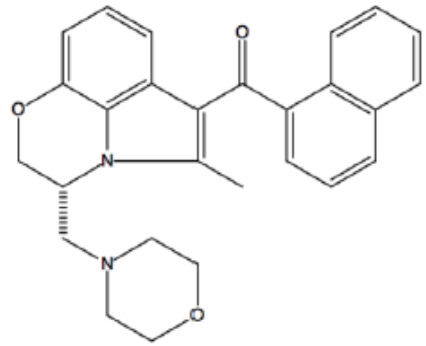
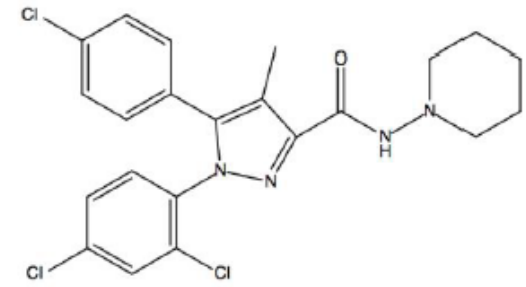


Δ9-tetrahydrocannabinol (THC)



Win 55, 212-2



Rimonabant

Legal Cannabinoid Delivery

- **Section 303 –**
- **Medical marijuana may only be dispensed in the following forms:**
  - **Pill**
  - **Oil**
  - **Topical forms**
  - **Form for vaporization**
  - **Tincture**
  - **Liquid**
- **Medical marijuana may not be dispensed to a patient in dry leaf or plant form.**
- **May not grow or prepare in edible form (flexibility at home)**

Legal Cannabinoid Delivery (in PA)

- **Section 303 –**
- **Medical marijuana may only be dispensed in the following forms:**
  - **Pill**
  - **Oil**
  - **Topical forms**
  - **Form for vaporization**
  - **Tincture**
  - **Liquid**
- **Medical marijuana may not be dispensed to a patient in dry leaf or plant form. Not anymore (as of April 16th, 2018)**
- **May not grow or prepare in edible form (flexibility at home)**

Supercritical CO_2 Extraction

- **Medicinal cannabinoids are very hydrophobic (lipophilic) compounds**
- Carbon dioxide usually behaves as a gas in air at standard temperature and pressure or as a solid called dry ice when frozen. If the temperature and pressure are both increased at or above the critical point for carbon dioxide it can adopt properties midway between a gas and a liquid. It behaves as a supercritical fluid above its critical temperature (87.98 °F) and critical pressure (72.9 atm), expanding to fill its container like a gas, but with a density like that of a liquid.

Dried Plant Material → Grind → Supercritical CO_2 Extraction → Winterize → Heat to Decarboxylate → **Plant Extract**

CBD	70.0 mg/ml
CBDV	1.14 mg/ml
Δ9-THC	1.59 mg/ml

Cannabinoid & Terpene Profile of Extracted Hemp

β-Caryophyllene	7373.8 ppm	Linalool	110.2 ppm
α-Humulene	2141.3 ppm	(-)-Caryophyllene Oxide	1458.0 ppm
(-) α-Bisabolol	138.9 ppm	Camphene	0.9 ppm
β-Myrcene	6.3 ppm	α-Terpinene	6.1 ppm
R (+) Limonene	6.6 ppm	Eucalyptol	25.1 ppm
Endo-Fenchyl Alcohol	166.4 ppm	ɣ-Terpinene	2.1 ppm
α-Terpineol	14.3 ppm	Fenchone	0.3 ppm
α-Pinene	0.5 ppm	Trans-Nerolidol	150.4 ppm

Dosages

- **Sativex (~2.5 mg THC and CBD)**
- **Dronabinol (2.5, 5.0, 10 mg THC)**
- **Typical dosages of medical marijuana in PA will be 10 mg of THC (in extracts)**
- **Diversion:**
  - **Low dose (esp. compared to marijuana cigarette)**
  - **Expensive**
  - **Centralized state-wide tracking**
  - **Combustible now available**

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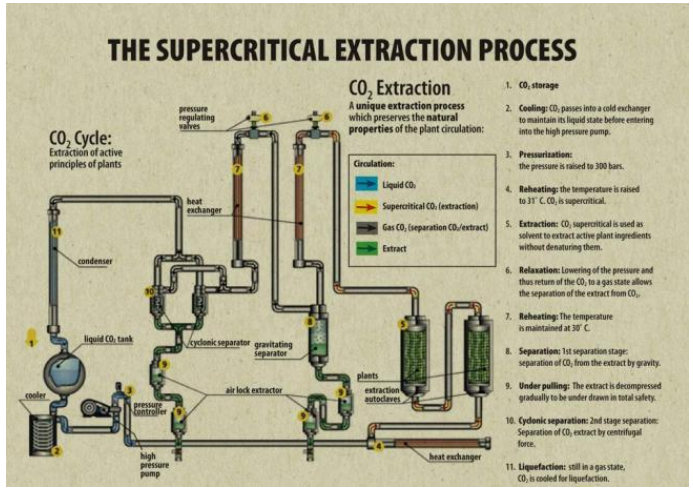
Permits



Permits

Certification (Card)

Certification (Card)

Recommendation

Two Public Health Concerns

1) CBG Oil
2) Delta-8-THC

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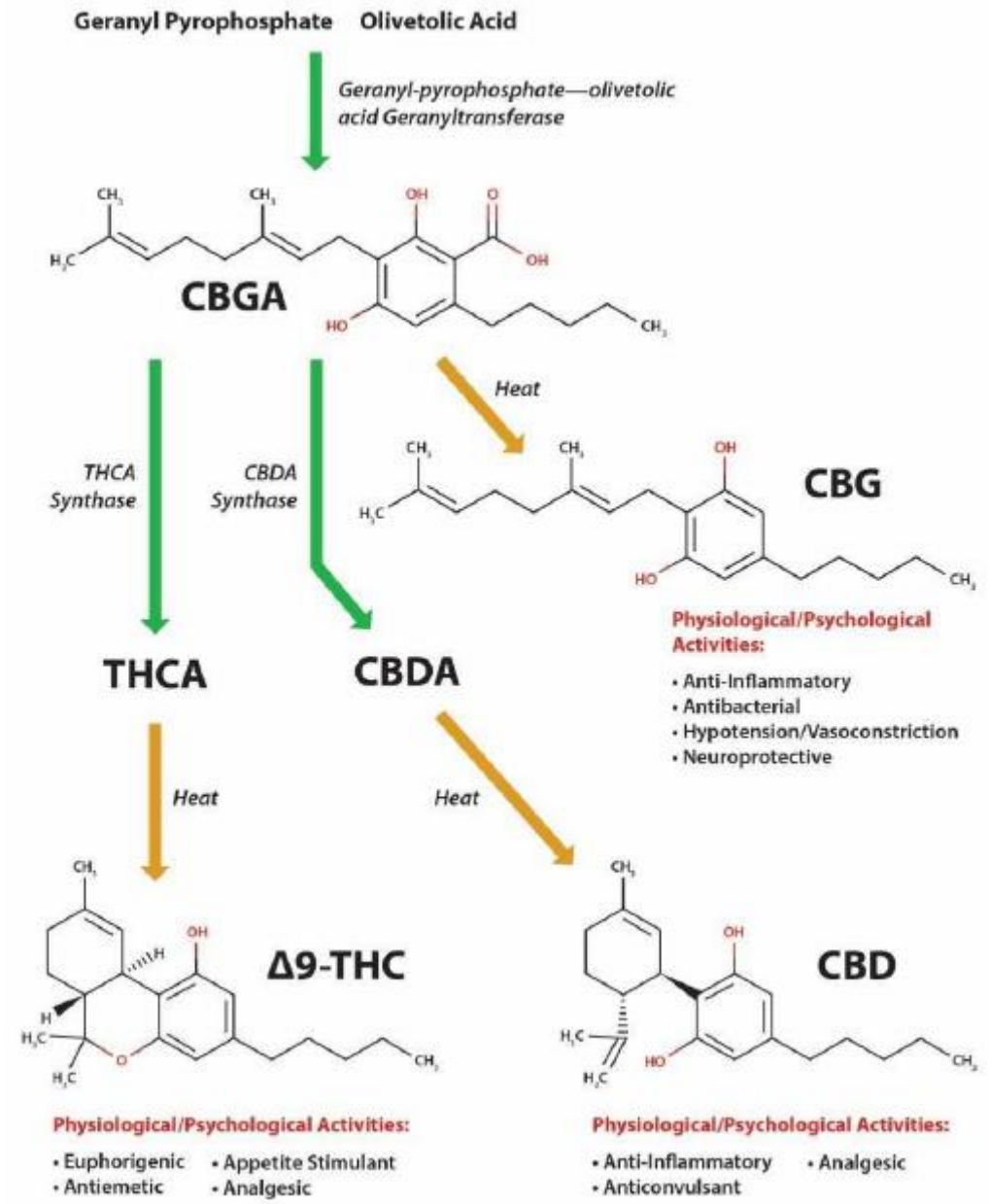
ASPET | THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

The Pharmacological Case for Cannabigerol

Rahul Nachnani, Wesley M. Raup-Konsavage and Kent E. Vrana

Journal of Pharmacology and Experimental Therapeutics February 2021, 376(2) 204-212; DOI: https://doi.org/10.1124/jpet.120.000340

Cannabigerol (CBG) & CBG Oil



Cannabigerol (CBG)

	THC		CBD		CBG	
Receptor	**Affinity (nM)**	**Function**	**Affinity (nM)**	**Function**	**Affinity (nM)**	**Function**
CB1	5.1-80.3 (Ki)	Partial Agonist	1458.5-4900 (Ki)	Inverse Agonist/ Antagonist	440-1045 (Ki)	Weak Agonist
CB2	3.1-75.3 (Ki)	Agonist	372.4-4200 (Ki)	Inverse Agonist	153.4-1225 (Ki)	Partial Agonist
GPR55	8 (EC50)	Agonist	445 (IC50)	Antagonist	N.T.	Unknown

Nachnani et al. JPET, 2020

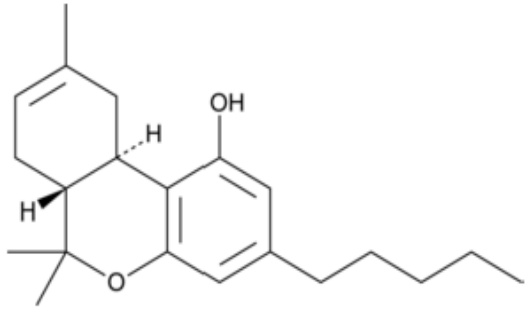
Cannabigerol (CBG)

	THC		CBD		CBG	
Receptor	**Affinity (nM)**	**Function**	**Affinity (nM)**	**Function**	**Affinity (nM)**	**Function**
α2-adrenoceptor	N.T.	Unknown	N.T.	Unknown	0.2-72.8	Agonist
5-HT_{1A}	N.T.	Unknown	N.D.	Indirect Agonist	51.9	Antagonist

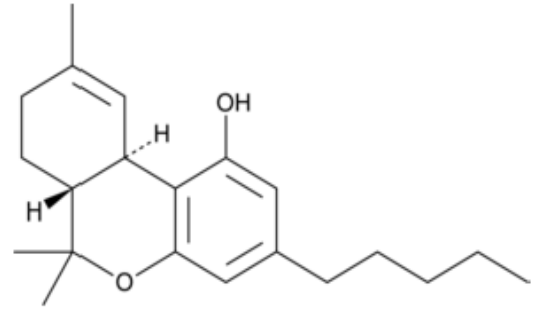
Delta-8 Tetrahydrocannabinol (Δ^8-THC)

A.

Δ^8-Tetrahydrocannbinol (THC)

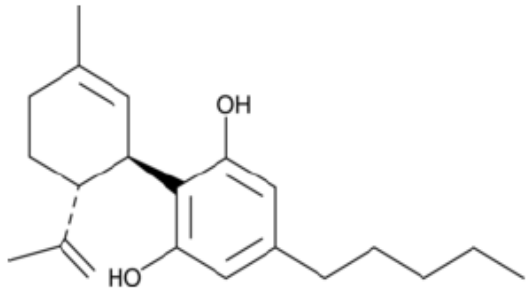


Δ^9-Tetrahydrocannbinol (THC)



44±12 nM	CB1	40.7±1.7 nM
44±17 nM	CB2	36±10 nM

B.

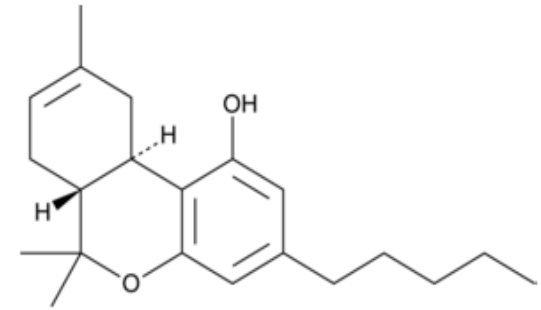


Cannabidiol (CBD)

Dissolve in Organic Solvent (i.e. Hexane)

Add acid & boil

Wash, Dry, & Test



Δ^8-Tetrahydrocannbinol (THC)

Research Initiatives at Penn State

- **Cannabinoids and Cancer (Lu, Vrana, and Yun)**
  - **Identifying cannabinoids that reduce cancer cell viability**
  - **Elucidating mechanisms**
- **Cannabinoids and Pain**
  - **Preclinical (ratios of THC:CBD) (Graziane and Kamal)**
    - **Acute Pain**
    - **Inflammatory Pain**
    - **Osteoarthritis**
    - **Neuropathic Pain**
  - **Clinical (Gordin, Thomas, and Deimling)**
    - **Opioid Limiting and Endometriosis Pain**
- **Cannabinoids and Novel Receptors and Pathways (Arnold, Mailman, and Dokholyan)**
- **Pharmacokinetics and Drug-Drug Interactions (Knehans, Raup-Konsavage, Kocis, Neighbors, and Vrana)**
- **Patient Outcomes Database (Leslie, and Vrana)**

Long Term Goals

- CBG Oil and THC Oil
- Endometriosis pain and CBD (Tim Deimling)
- Clinical pain trial, opioid-sparing
- Evaluating optimum ratios of THC:CBD for pain, anxiety, PTSD, other disorders (preclinical)
- Cannabinoids to treat opioid addiction
- Continuing to monitor and identify Drug-Drug Interactions
  - Mobile App (Paul Kocis and Penn State-Harrisburg)
- Pharmacokinetics of topical cannabinoids
- Begin exploring relationships between genetics and outcomes (personalized medicine)
- Graduate Student Fellowship Program
  - Launching, May, 2021
- Potential undergraduate degree or certificate program

Cannabis and Cannabinoid Research
Volume 3.1, 2018
DOI: 10.1089/can.2018.0065

Cannabis and Cannabinoid Research

Mary Ann Liebert, Inc. publishers

ORIGINAL RESEARCH

Open Access

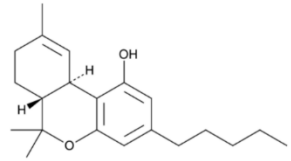
Synthetic Cannabinoid Activity Against Colorectal Cancer Cells

Wesley M. Raup-Konsavage,[1] Megan Johnson,[1] Christopher A. Legare,[1] Gregory S. Yochum,[2] Daniel J. Morgan,[1,3] and Kent E. Vrana[1,*]

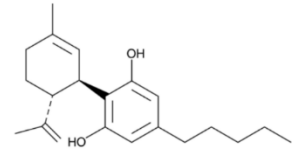
Raup-Konsavage et al. (2018) Cannabis Cannabinoid Res

Compound	SW480	SW620	HT29	DLD-1	HCT116	LS174	RKO
CBD	16.4±0.6	n.d.	23.0±4.4	19.8±1.4	n.d.	n.d.	n.d.
HU-331	5.5±1.6	11.1±2.5	17.0±3.2	7.8±1.8	11.0±4.2	8.36±2.3	10.4±2.1
(±)-5-epi CP 55,940	6.5±1.6	8.1±1.0	7.3±1.0	5.3±0.04	4.9±0.5	6.2±0.5	5.9±0.5
(±) CP 55,940	25.1±3.1	26.8±2.7	21.3±5.5	21.7±2.6	16.2±5.6	16.3±2.2	14.9±1.7
(+) CP 55,940	24.4±5.6	31.1±3.5	24.1±4.6	16.0±1.2	16.8±4.0	16.9±3.6	19.0±3.3
(-) CP 47,497	8.9±0.1	16.5±6.5	24.6±5.7	12.6±2.3	14.7±0.02	23.0±6.1	19.8±4.4
(±) 3-epi CP 47,497 C-8 Homolog	8.9±1.7	13.5±1.4	14.2±5.0	12.4±2.0	12.6±1.5	12.2±0.9	15.0±2.8
(±) CP 47,497 C-8 Homolog	n.d.	n.d.	20.1±4.2	33.4±1.8	32.0±1.8	21.7±6.1	39.0±5.6
PTI-1	11.9±2.3	19.6±0.2	14.4±2.4	19.4±1.1	21.2±5.5	25.0±3.6	27.5±2.7
PTI-2	7.4±1.4	23.9±3.6	8.2±1.6	34.2±7.8	27.7±3.1	n.d.	15.6±2.9
NPB-22	9.7±0.6	n.d.	n.d.	n.d.	15.2±6.3	n.d.	n.d.

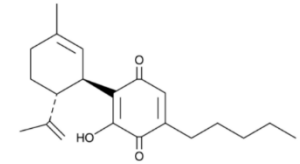
Compound	SW480	SW620	HT29	DLD-1	HCT116	LS174	RKO
CBD	16.4±0.6	n.d.	23.0±4.4	19.8±1.4	n.d.	n.d.	n.d.
HU-331	5.5±1.6	11.1±2.5	17.0±3.2	7.8±1.8	11.0±4.2	8.36±2.3	10.4±2.1
(±)-5-epi CP 55,940	6.5±1.6	8.1±1.0	7.3±1.0	5.3±0.04	4.9±0.5	6.2±0.5	5.9±0.5
(±) CP 55,940	25.1±3.1	26.8±2.7	21.3±5.5	21.7±2.6	16.2±5.6	16.3±2.2	14.9±1.7
(+) CP 55,940	24.4±5.6	31.1±3.5	24.1±4.6	16.0±1.2	16.8±4.0	16.9±3.6	19.0±3.3
(-) CP 47,497	8.9±0.1	16.5±6.5	24.6±5.7	12.6±2.3	14.7±0.02	23.0±6.1	19.8±4.4
(±) 3-epi CP 47,497 C-8 Homolog	8.9±1.7	13.5±1.4	14.2±5.0	12.4±2.0	12.6±1.5	12.2±0.9	15.0±2.8
(±) CP 47,497 C-8 Homolog	n.d.	n.d.	20.1±4.2	33.4±1.8	32.0±1.8	21.7±6.1	39.0±5.6
PTI-1	11.9±2.3	19.6±0.2	14.4±2.4	19.4±1.1	21.2±5.5	25.0±3.6	27.5±2.7
PTI-2	7.4±1.4	23.9±3.6	8.2±1.6	34.2±7.8	27.7±3.1	n.d.	15.6±2.9
NPB-22	9.7±0.6	n.d.	n.d.	n.d.	15.2±6.3	n.d.	n.d.



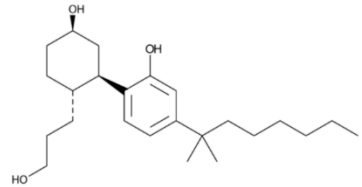
Δ^9-THC



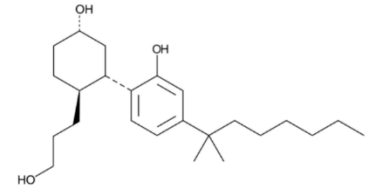
CBD



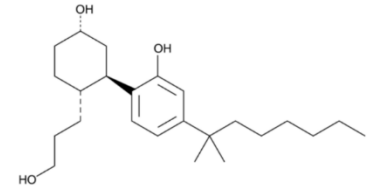
HU-331



(±) CP 55,940



(+) CP 55,940



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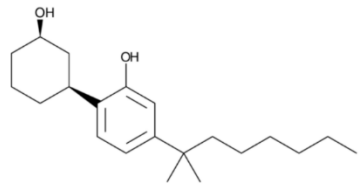
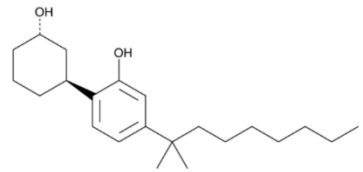


(-) CP 47,497



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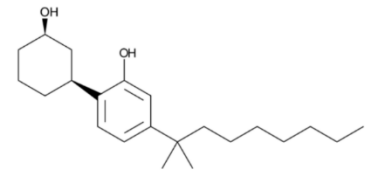
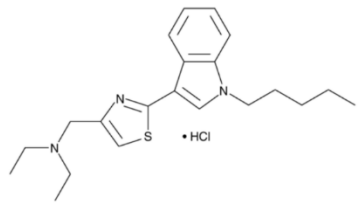
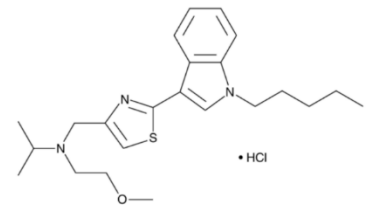


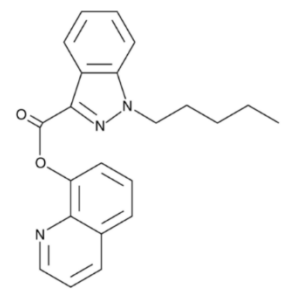
(±) CP 47,497 C-8 Homolog



PTI-1



PTI-2



NPB-22

Figure 6

Medical Cannabis and Cannabinoids

Legal and Regulatory Aspects – Commentary

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The Trouble with CBD Oil

Arno Hazekamp

Hazekamp Herbal Consulting, Leiden, The Netherlands

Table 1. Analysis of Dutch cannabis oil samples obtained from actual patients, comparing the claimed cannabinoid content on the product label with lab results measured in the study [51]

Sample ID	CBD(A)			THC(A)		
	label, %	measured, %	deviation, rel. %	label, %	measured, %	deviation, rel. %
1	**27**	2.3	*–91.5*	**17**	0.1	*–99.4*
2	**25**	0	*–100*	**35**	4.6	*–86.9*
3	**12**	0.2	*–98.3*	–	0	*
4	**10.9**	2.8	*–74.3*	–	0.1	*
5	**10**	2.2	*–78*	**10**	4	*–60*
6	**8**	0.6	*–92.5*	**4**	0.2	*–95*
7	**8**	0.6	*–92.5*	**4**	0.1	*–97.5*
8	**6**	0.2	*–96.7*	**5**	0.1	*–98*
9	**5**	0	*–100*	**40**	3.4	*–91.5*
				–	0.2	*
11	**4**	5.4	*+35*	–	0.3	*
12	**4**	4	*0*	–	0	*
13	**4**	4.2	*+5*	–	0	*
14	**3**	3.1	*+3.3*	–	0.2	*
15	**2.75**	2.8	*+1.8*	–	0.1	*
16	**0.1**	0.1	*0*	**4**	6.3	*+57.5*
17	–	0.1	*	**7**	7.9	*+12.9*
18	–	0	*	**5**	0.7	*–86*
19	–	0	*	**5**	0.9	*–82*
20	–	0.1	*	**20**	15.8	*–21*
21	–	0	*	**7**	6.4	*–8.6*

CBD, cannabidiol; THC, tetrahydrocannabinol; CBD(A), total sum of CBD plus CBD-acid; THC(A), total sum of THC plus THC-acid. * Not applicable because no label claim was made.

MEDICAL CANNABIS AND CANNABINOIDS

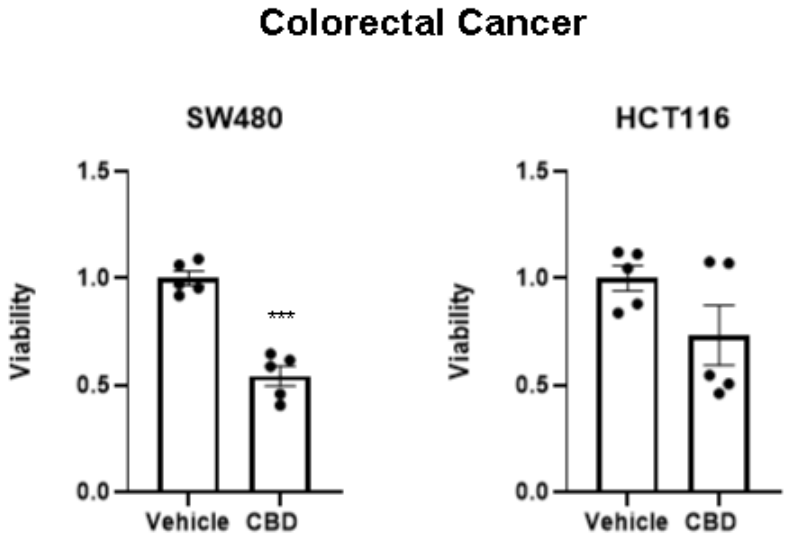
Cannabidiol (CBD) Oil Does Not Display an Entourage Effect in Reducing Cancer Cell Viability In Vitro

Wesley M. Raup-Konsavage, Nurgul Carkaci-Salli, Kelly Greenland,
Robert Gearheart Jr., Kent E. Vrana

Med Cannabis Cannabinoids 2020;3:95–102

CBD Variably Reduces Cancer Cell Viability

A.



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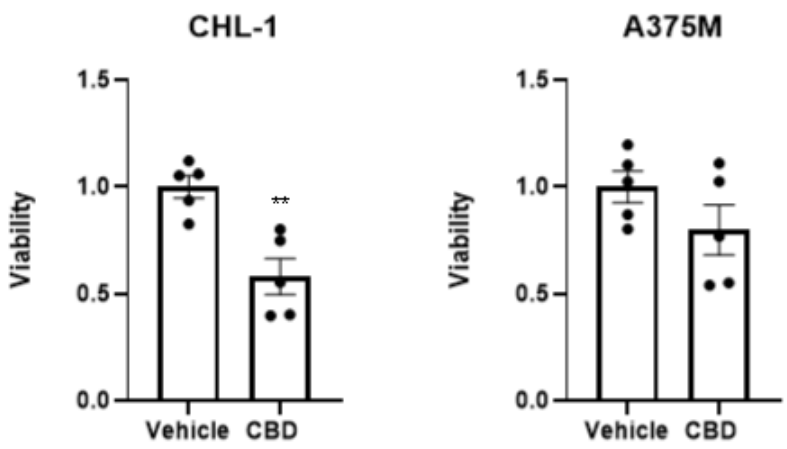

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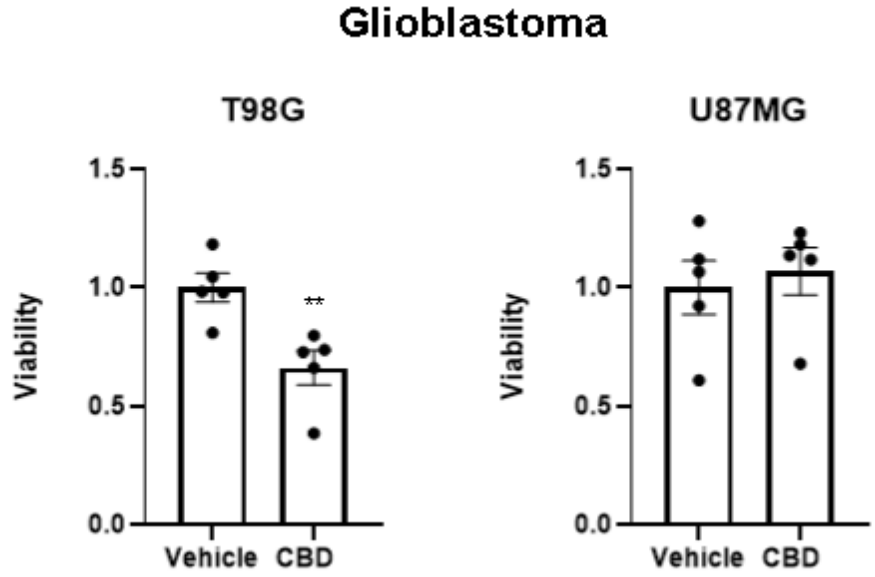
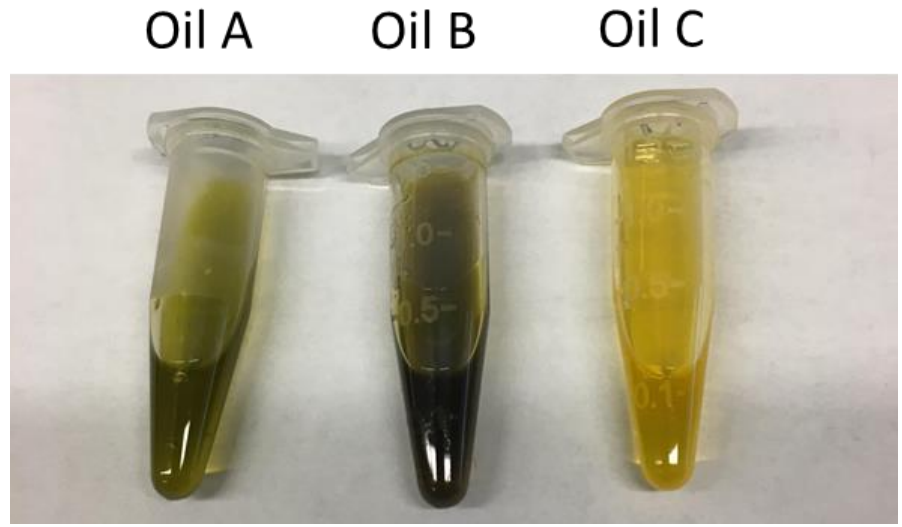


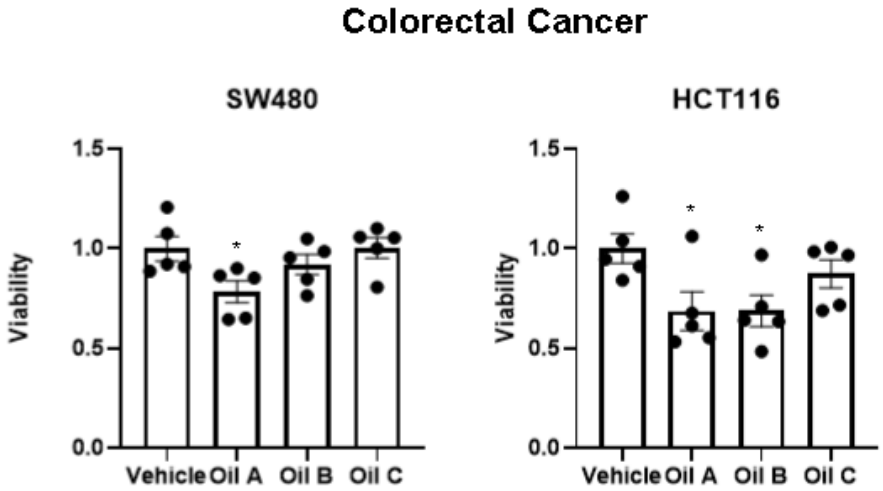
Comparison of CBD Oils



Pigment	Wavelength	Oil A	Oil B	Oil C
Chlorophyll a	430 nm	0.21	0.57	0.08
Chlorophyll b	453 nm	0.14	0.37	0.09
Carotenoids	500 nm	0.06	0.16	0.05

CBD Oils Have Variable Potencies or Efficacies

A.



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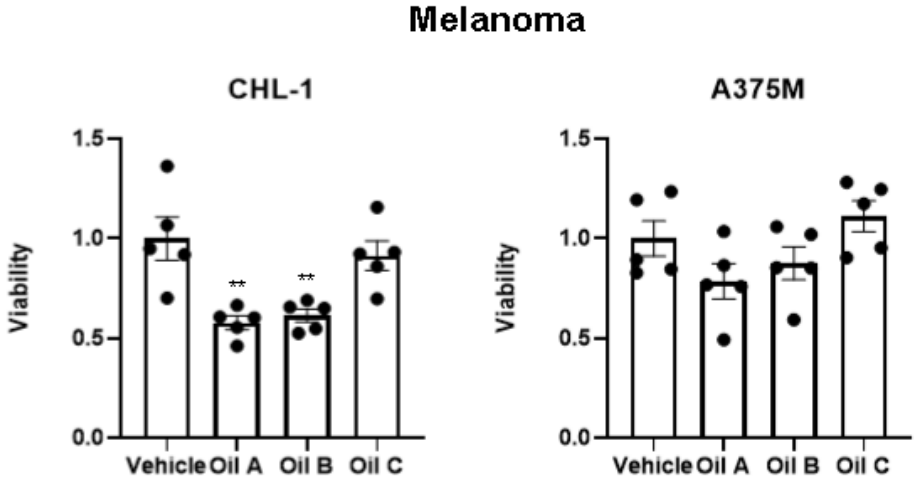

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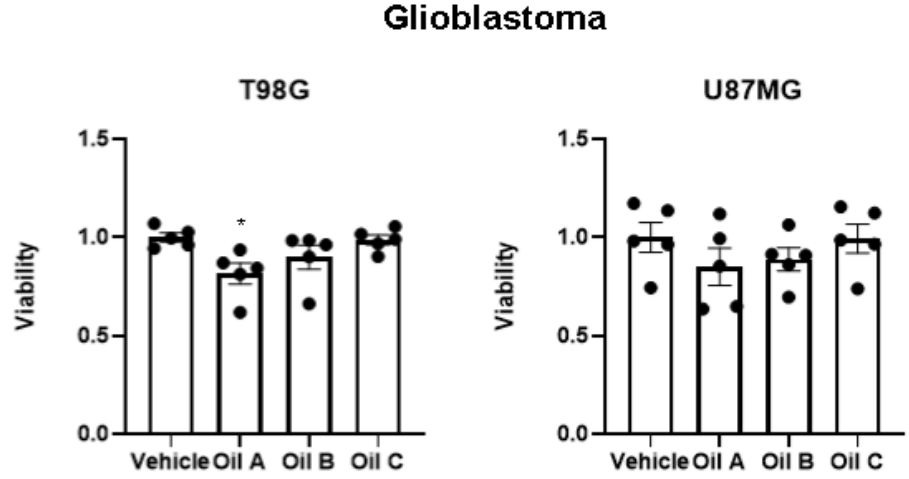
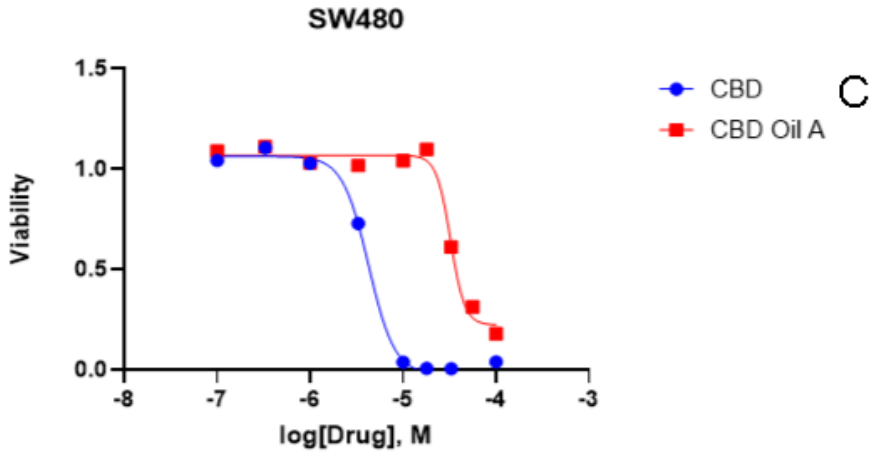


No CBD Oil is More Potent than Pure CBD

A.



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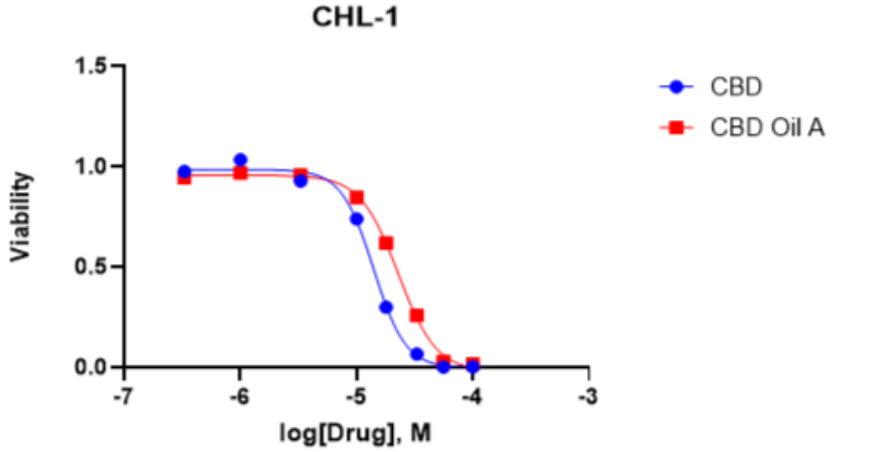

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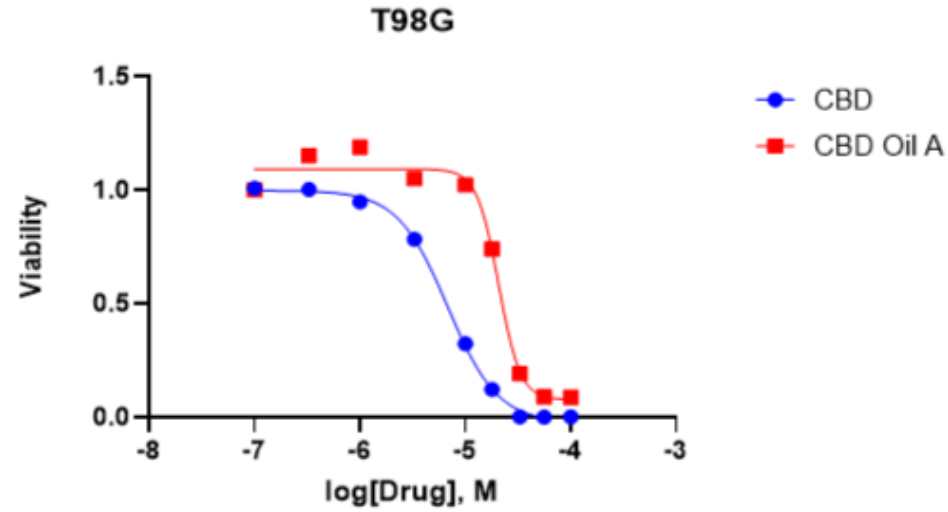

Cell Line	CBD IC50	Oil A IC50
SW480	5.8 ± 2.6 µM *	36.8 ± 5.6 µM
HCT116	8.0 ± 4.8 µM	25.5 ± 8.3 µM
CHL-1	16.6 ± 3.2 µM	23.5 ± 1.7 µM
A375M	14.1 ± 1.2 µM	25.1 ± 1.6 µM
T98G	10.4 ± 1.9 µM	19.1 ± 2.7 µM
U87MG	17.8 ± 1.5 µM	18.1 ± 2.0 µM

Medical Cannabis and Cannabinoids

Preclinical Science and Clinical Studies – Review Article

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Delta-9-Tetrahydrocannabinol and Cannabidiol Drug-Drug Interactions

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sites.psu.edu/cannabinoid

Penn State College of Medicine, Dept of Pharmacology

One of the objectives of this website, and associated journal article, is to develop a comprehensive and detailed cannabinoid drug-drug interaction list aligned with regulatory approved prescribing information. Also, as newer medications are approved, and real-world evidence accumulates, another objective is to routinely update this drug-drug interaction list.

The following cannabinoid drug-drug interaction information is predicated on regulatory agency approved cannabinoid manufacturer prescribing information, and then supplemented with the FDA *'Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers'* online document and the DrugBank database.

Narrow Therapeutic Index (NTI) Medications to be Closely Monitored when Coadministered with Cannabinoids

We have identified a list of 57 prescription medications displaying a narrow therapeutic index that are potentially impacted by concomitant cannabinoid use (whether through prescription use of cannabinoid medications or recreational/medical use of cannabis and its extracts).

Information on these 57 NTI medications can be accessed via this hyperlink:

Delta-9-THC and Cannabidiol DDI – Table 2 – Updated 2020_08_17

Table 2. List of Narrow Therapeutic Index (NTI) medications to be closely monitored when coadministered with cannabinoids, either therapeutically or recreationally

Narrow Therapeutic Index (NTI) medication	Enzyme/metabolism
acenocoumarol (VKA)	CYP1A2, CYP2C9, CYP2C19, CYP3A4
alfentanil	CYP3A, CYP3A4
aminophylline	CYP1A2, CYP3A4
amiodarone	CYP1A2, CYP2C8, CYP2C19, CYP3A4
amitriptyline	CYP1A2, CYP2B6, CYP2C19, CYP3A4
amphotericin B	Protein binding
argatroban	CYP3A4
busulfan	CYP3A4
carbamazepine	CYP1A2, CYP3A4, UGT2B7
clindamycin	CYP3A4
clomipramine	CYP1A2, CYP2B6, CYP2C19, CYP3A4, UGT2B7
clonidine	CYP1A2, CYP3A4
clorindione (VKA)	CYP3A4
cyclobenzaprine	CYP1A2, CYP3A4
cyclosporine	CYP3A4
dabigatran etexilate	UGT1A9, UGT2B7
desipramine	CYP1A2, CYP2B6
dicoumarol (VKA)	CYP2C9
digitoxin	CYP3A4
dihydroergotamine	CYP3A4
diphenadione (VKA)	CYP3A4
dofetilide	CYP3A4
dosulepin	CYP2B6
doxepin	CYP1A2, CYP2C9, CYP2C19, CYP3A4
ergotamine	CYP3A4
esketamine	CYP2B6, CYP3A4
ethinyl estradiol (oral contraceptives)	UGT1A9, UGT2B7
ethosuximide	CYP2E1, CYP3A4
ethyl biscoumacetate (VKA)	CYP3A4
everolimus	CYP3A, CYP3A4
fentanyl	CYP3A4
fluindione (VKA)	CYP2C9, CYP3A4
fosphenytoin	CYP2C8, CYP2C9, CYP2C19, CYP3A4
imipramine	CYP1A2, CYP2B6, CYP2C19, CYP3A4
levothyroxine	CYP3A4
lofepramine	CYP2B6
melitracen	CYP2B6
meperidine	CYP2B6, CYP3A4
mephenytoin	CYP1A2, CYP2C19
mycophenolic acid	UGT1A9, UGT2B7
nortriptyline	CYP1A2, CYP2B6, CYP3A4
paclitaxel	CYP2C8, CYP3A4
phenobarbital	CYP2C19
phenprocoumon (VKA)	CYP2C8, CYP2C9, CYP3A4
phenytoin	CYP2C8, CYP2C9, CYP2C19
pimozide	CYP1A2, CYP3A, CYP3A4
propofol	UGT1A9
quinidine	CYP2C9, CYP2E1, CYP3A4
sirolimus	CYP3A, CYP3A4
tacrolimus	CYP3A, CYP3A4
temsirolimus	CYP3A4
theophylline	CYP1A2, CYP3A4
thiopental	CYP2C19
tianeptine	CYP3A4
trimipramine	CYP2B6
valproic acid	CYP2C9, UGT1A9, UGT2B7
warfarin (VKA)	CYP1A2, CYP2C9, CYP2C19, CYP3A4

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- Wesley Raup-Konsavage, PhD
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- Greg Yochum, PhD
- Dan Morgan, PhD
- Richard Mailman, PhD
- Johnny Lu, PhD
- Jung Yun, PhD
- Amy Arnold, PhD
- Yuval Silberman, PhD
- Kelly Greenland, PhD and Robert Gearhart

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Questions?

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