CBD & MARIJUANA DERIVATIVES IN MEDICINE

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Disclosures

- I have no relevant financial relationships to disclose.

Objectives

At the conclusion of this presentation, attendees should be able to:

- Better understand the Endocannabinoid System
- Compare and contrast the effects of some of the cannabis derivatives
- Identify safety considerations for patients using medical marijuana or CBD
- Be aware of some of the current basic research pertinent to these marijuana derivatives

CANNABIS

- **> 500 chemicals**
- **> 140 cannabinoid compounds**

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The Cannabis Players

- **Cannabinol**
- **Cannabigerol**
- **Cannabidiol**
- **9-Tetrahydrocannibinol**
- **Tetrahydrocannabivarin**
- **Tetrahydrocannabinolic Acid**

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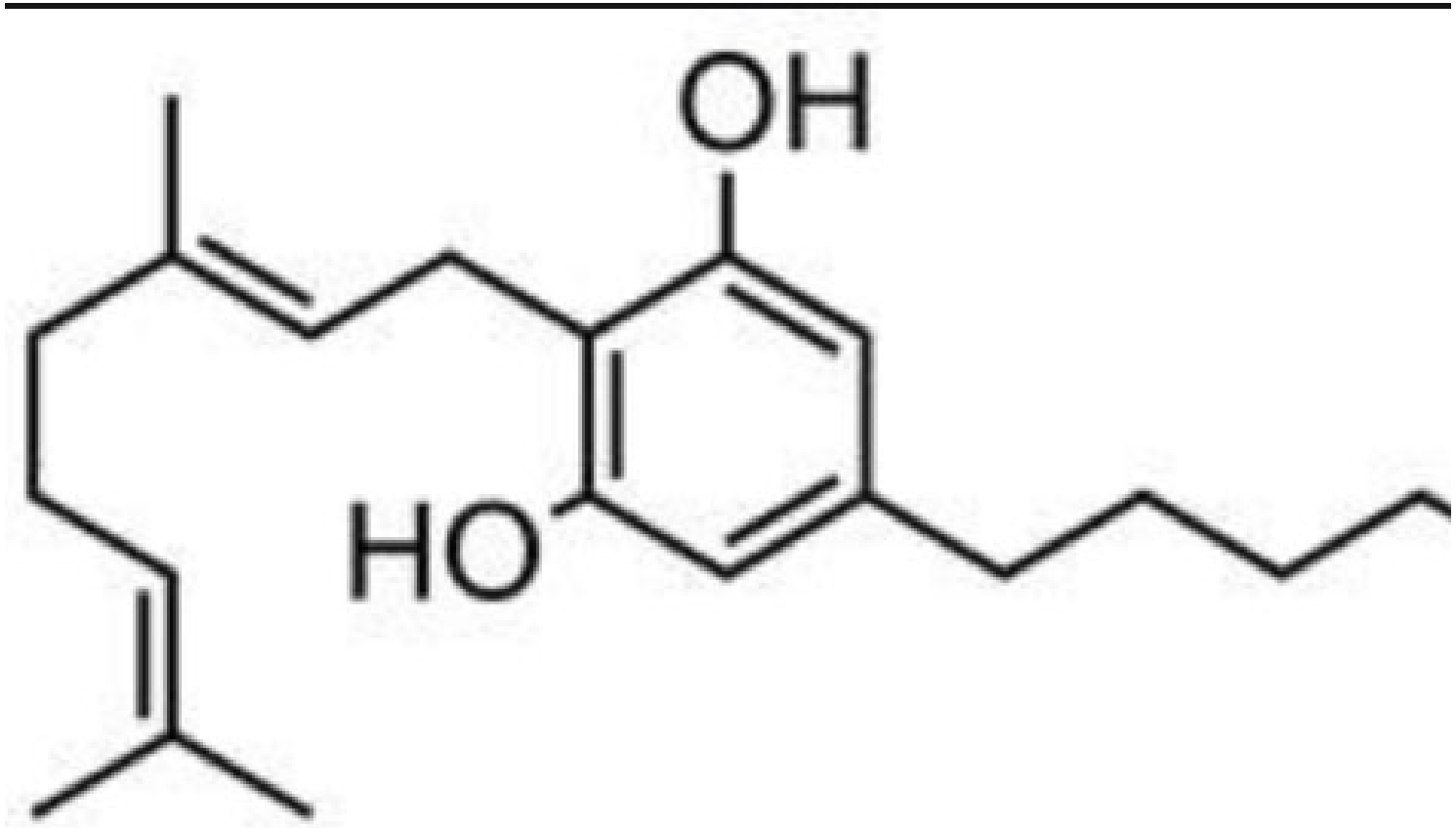

Cannabigerol (CBG)

- PubChem CID # 5315659
- Only 1% of cannabinoids in plant, but precursor for all the others.
- As of 2019 no human research has been conducted
- Evaluation in lab models of colitis show beneficial effect
- Antagonizes CB1R and 5HT1A, but agonist at α2 receptor

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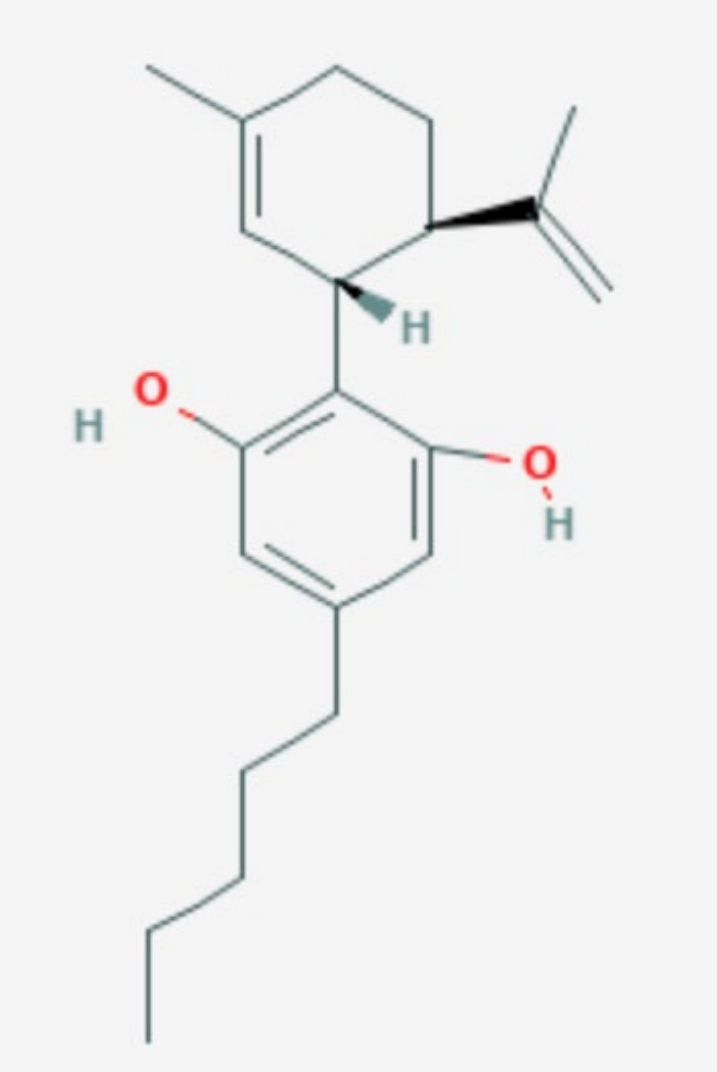
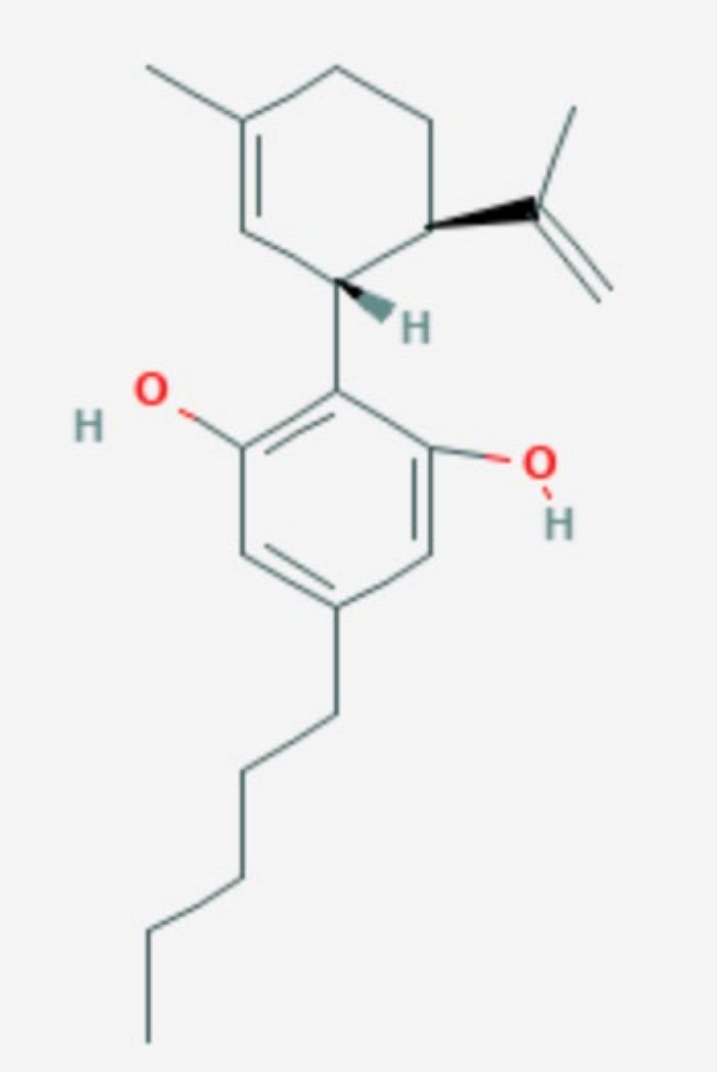


Cannabidiol (CBD)

- 40% of the total cannabis extract
- Oral bioavailability = 15%
- Inhaled 30% bioavailable
- T1/2 = 18 – 30 h
- Epidiolex FDA approved (10mg/kg/day; BID)
- PubChem CID #644019



Cannabidiol (CBD)

- Activates: 5HT1A/2A/3A serotonin receptors; TRPV1-2 vanilloid receptors; PPARγ
- Blocks T-type calcium channels
- Antagonizes α1 adrenergic and μ-opioid receptors
- Inhibits synaptosomal uptake of: norepinephrine, dopamine, serotonin, and GABA
- Stimulates activity of the inhibitory glycine receptor

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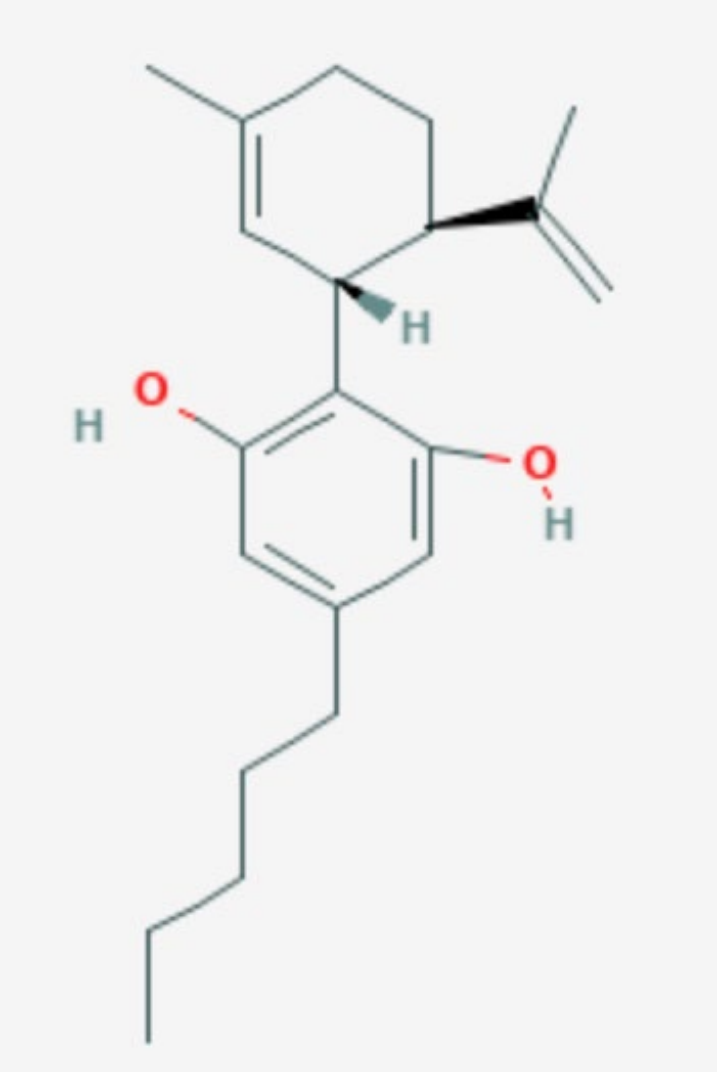

Cannabidiol (CBD)

- Analgesic
- Anti-inflammatory
- Anti-neoplastic
- Anti-proliferative**
- Anti-angiogenic**
- Pro-apoptotic**

** Not thru CB1 or CB2 or vanilloid receptor

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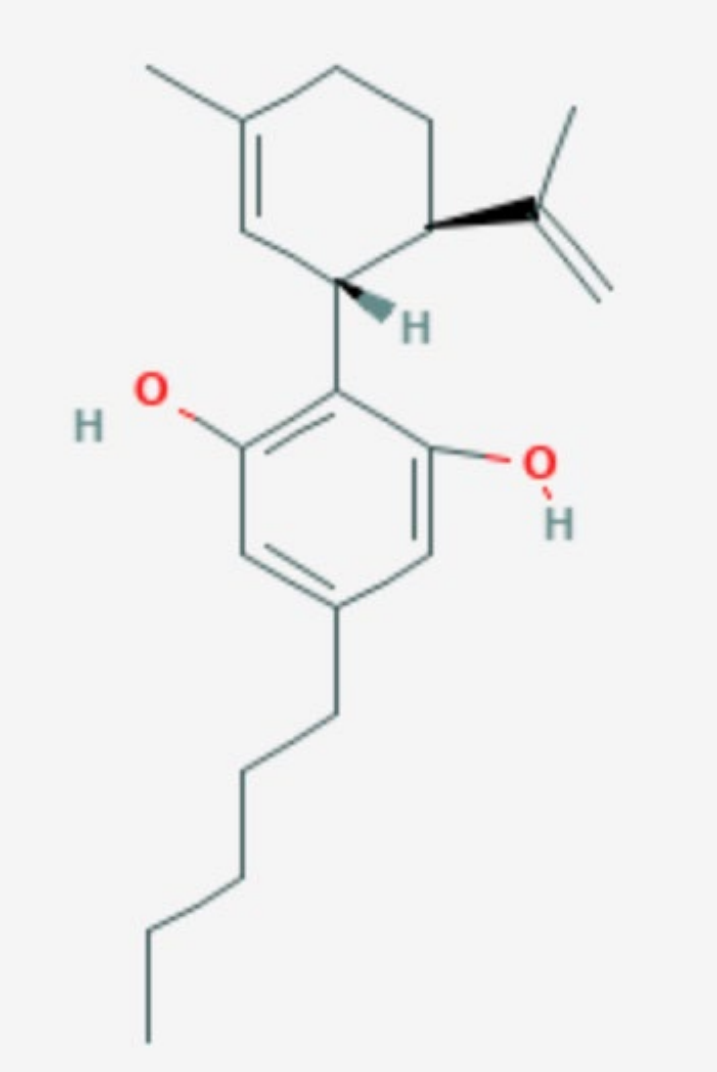
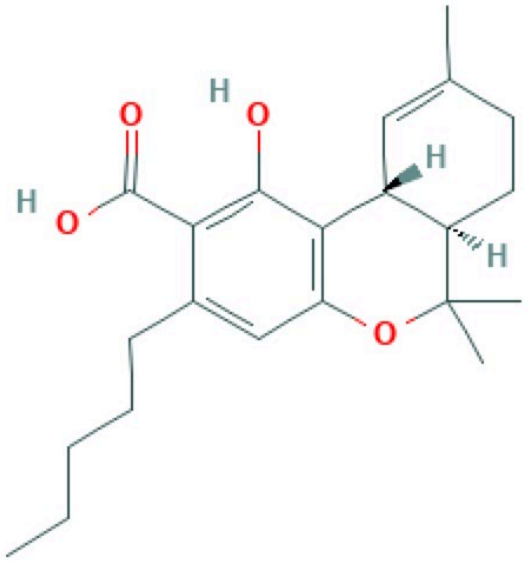


Cannabidiol (CBD)

- Stimulates endoplasmic reticulum (ER) stress signaling.
- Inhibits AKT/mTOR signaling; thereby activating autophagy and apoptosis.
- Enhances generation of ROS
- Decreases expression of the inhibitor of DNA-binding 1 (ID-1)
- Activates TRPV2; thereby increasing uptake of cytotoxic agents in cancer cells
- Upregulates expression of ICAM-1 and TIMP-1; thereby inhibiting metastases and cancer cell invasiveness.

Tetrahydrocannabinolic acid (THCA)



- Two isomers: THCA-A & THCA-B
- PubChem CID #98523
- Decarboxylates to Δ1-THC, then to Δ9-THC
- Strongly Activates PPARγ
- Suppresses COX-2 and MMP9 gene expression

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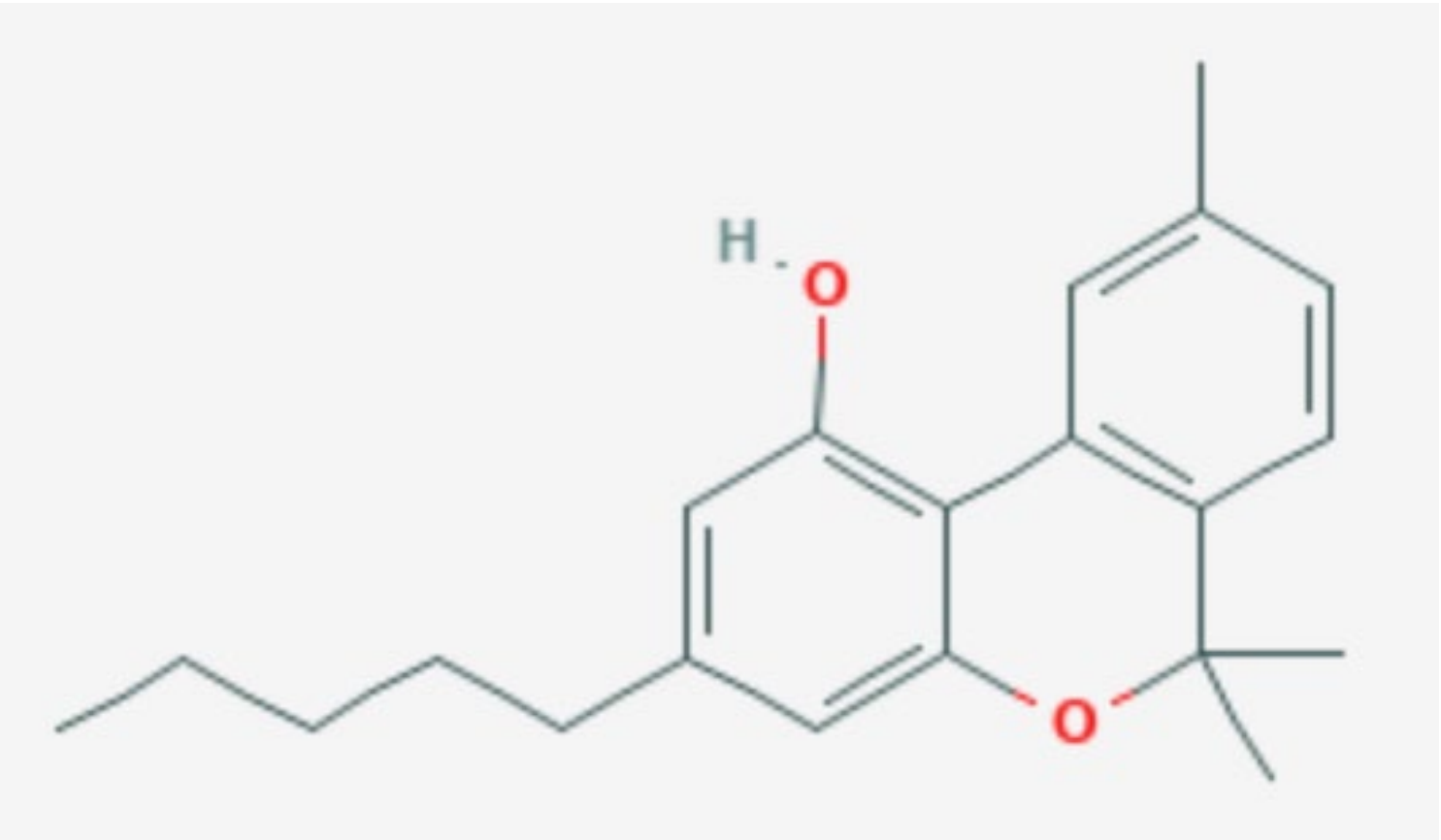

Cannabinol (CBN)

- Formed as a metabolite of THC and THCA
- Only 10% as THC
- Affinity for CB2 > CB1

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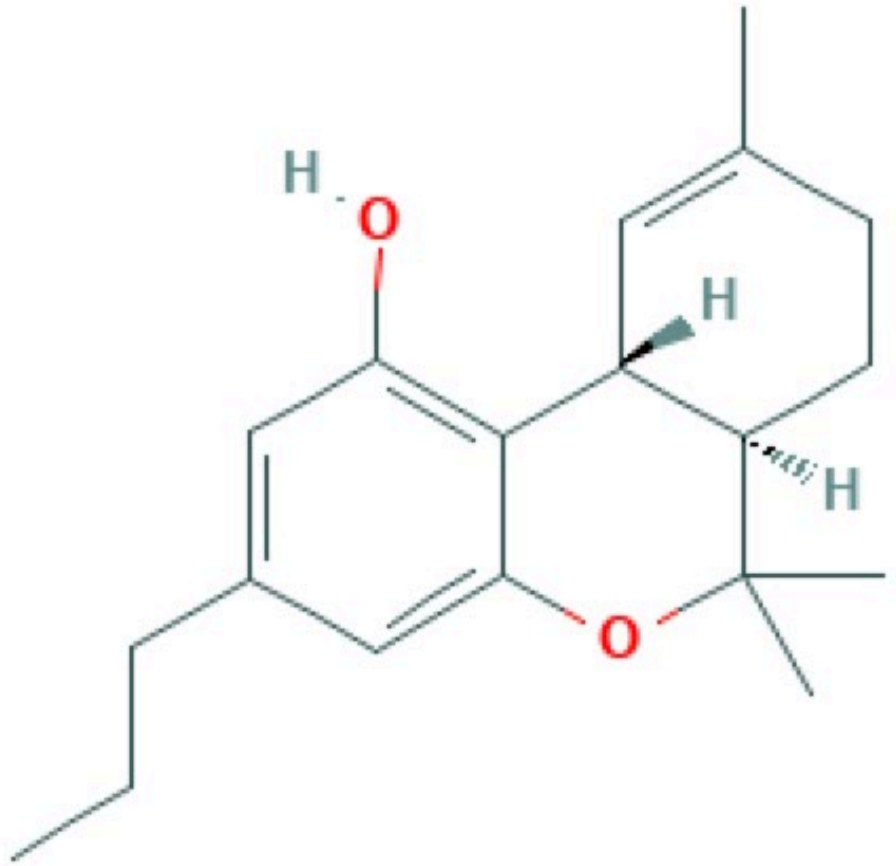
Tetrahydrocannabivarin (THCV)

- Propyl analogue of THC
- Pub Chem CID #34180
- May be up to 50% 0f total cannabinoids in some Indica sp.
- CB1R antagonist
- CB2R partial agonist
- Partial & selective PPARγ modulator



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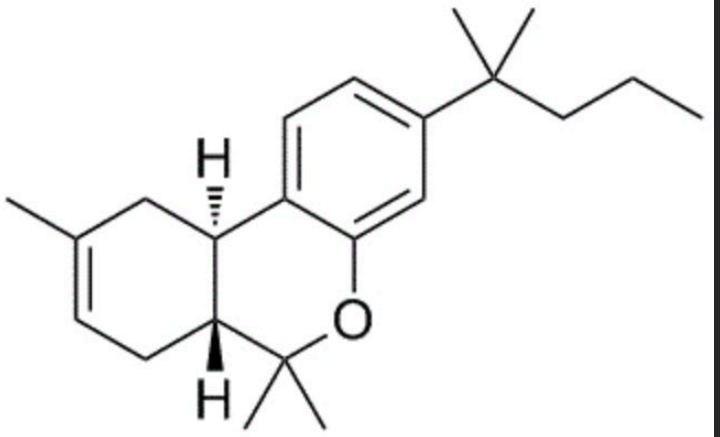
Synthetic Cannabinoids

- **> 350 synthetic compounds acting on the endocannabinoid system have been developed**

Synthetic Cannabinoids



- JWH 133 : potent CB2R agonist
- JWH 018 : full CB1R & CB2R agonist
- JWH 073
- WIN 55,212-2
- HU 210 : 100-800x more potent than THC
- HU-211 : Enantiomer of HU-210, but inactive at CB1R & CB2R. Potent NMDA antagonist.
- HU 239 : ajulemic acid

Medical Marijuana in Pennsylvania

- **At least 20 approved/legal conditions**
- **> 1000 physicians providing usage**
- **Competing dispensaries with on-line menus**

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Regulated Medical Marijuana

- Highly regulated
- Good quality controls
- Legal, kind-of
- Specific quantity of THC/CBD
- Menu On-line
- Expensive

Disposables | Indica

BHO- HONEY BOO

CRESCO

This indica dominant strain will tackle stress, insomnia, and pain. THC: 76.256%, THCa: 0.278%, THCv: 0.592%, CBD: 0.222%, CBN: 0.202%, CBG: 3.554%, CBC: 0.916% / b-Carophyllene: 1.549%, b-Myrcene: 1.220%, a-Pinene: 0.842%

$30 1/4 gram

Disposables | Hybrid

CO2 - BREATHE 2:1 (THC:CBD)

ILERA

Breathe is formulated to provide a sense of calm and decreased anxiety. Breathe's unique terpene and cannabinoid profile, which is high in Linalool and Terpinolene, leaves you feeling relaxed and not overly sleepy. THC: 49.180%, CBD: 28.629% / Terpinolene: 3.038%, Linalool: 0.984%, Humulene: 0.217%

$30 1/4 gram

Oil | Hybrid

RSO - HARLEQUIN 1:1

CRESCO

Balanced in CBD and THC this strain can relax without sedation and provide clear-headed, alert effects. It is regarded as an excellent reliever of pain, either associated with the body and muscles. THC: 41.740%, THCa: 0.146%, CBD: 43.091%, CBDa: 0.239%, CBDv: 0.429%, CBN: 0.509%, CBG: 2.635%, CBC: 2.417% / b-Carophyllene: 0.362%, Bisabolol: 0.159%, Humulene: 0.118%

$75 gram

Capsules | Hybrid

IREM 5:1 (CBD:THC) - 20 COUNT

TERRAPIN

The iREM 5:1 is a high CBD line that is excellent for insomnia. It provides improved ability to fall asleep and stay asleep, mood improvement and relaxation. The CBD in this blend will calm the psychoactive effect of the THC. 2.97 mg THC : 19.92 mg CBD per Capsule

$60 each

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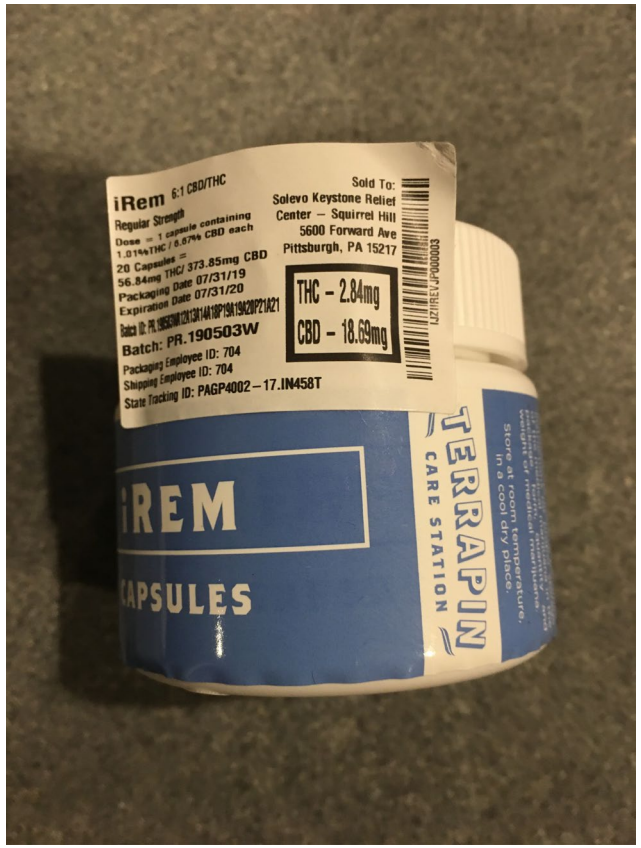
Medical Marijuana



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Unregulated CBD Products

- Hemp products are unregulated.
- Easy to buy
- Not Expensive
- Legal
- Poor quality controls. JAMA 2017; 318(17): 1708-1709. 69% of CBD products mislabeled. 22% also contained THC.

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Common CBD Side Effects

- Lightheadedness
- Drowsiness
- Diarrhea
- No desired effect

- Fatigue
- Nausea
- Irritability
- Increase INR if on warfarin

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CBD and CYTOCHROME P450

CYP3A4 Inhibitors

- Strong: protease inhibitors; ketoconazole; loperamide
- Moderate: amiodarone; verapamil; aprepitant; imatinib

- Causes increased CBD availability. Therefore, Reduce CBD dose

CYP3A4 Inducers

- Strong: phenytoin; enzalutamide
- Moderate: carbamazepine; topiramate; phenobarbital; pioglitazone; efavirenz

- Decreases CBD bioavailability. Therefore, increase CBD dose.

CBD and CYTOCHROME P450

CYP2C19 Inhibitors

- Strong: fluvoxamine; fluoxetine
- Moderate: PPIs; clopidogrel; fluconazole; efavirenz

- Cause increased CBD availability and risk of side effects; therefore, reduce CBD dose

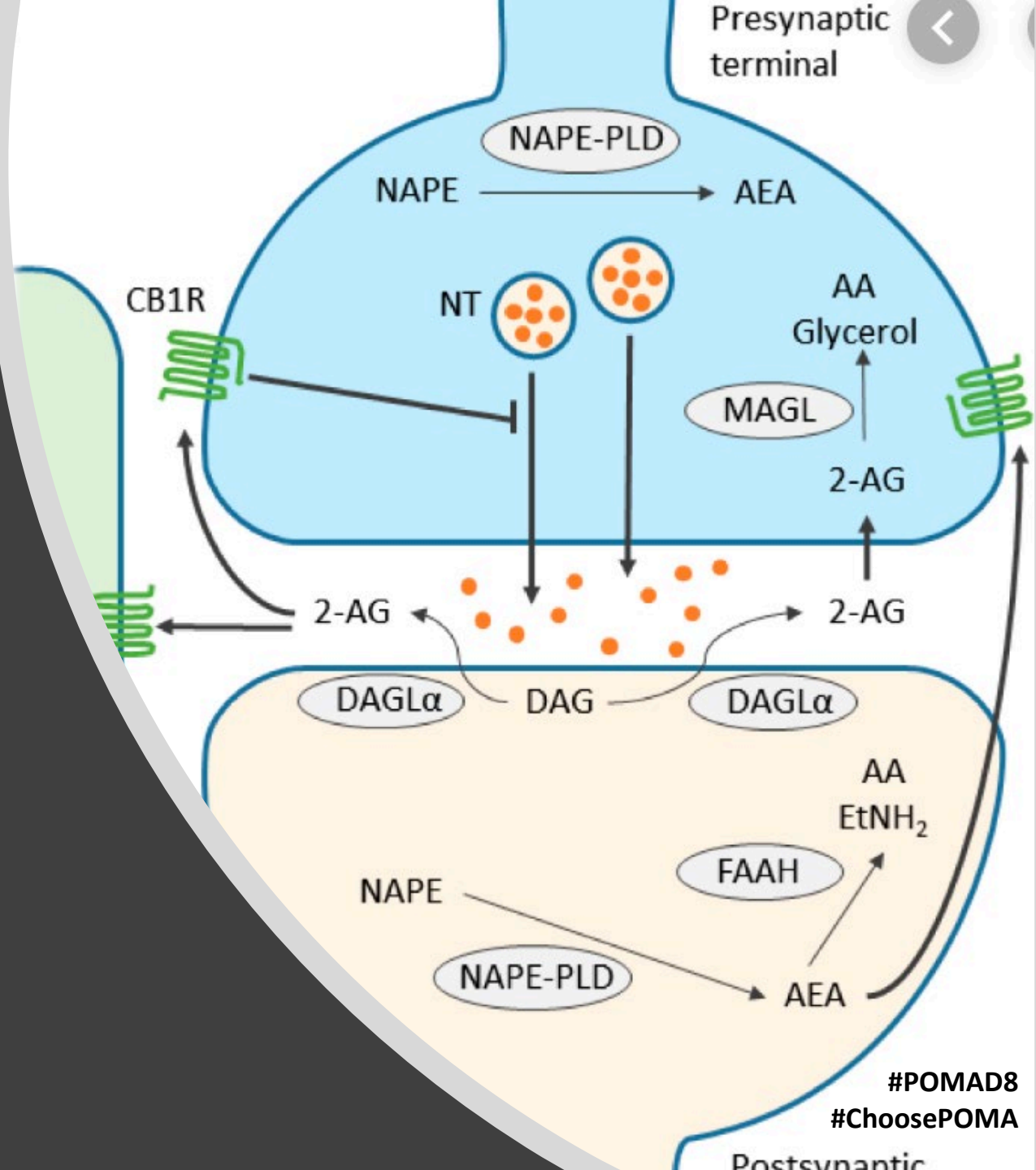
CYP2C19 Inducers

- Rifampin; carbamazepine; phenobarbital; phenytoin

- Will result in decreased CBD bioavailability; therefore, consider increasing CBD dose

Endocannabinoid Receptor System

- THC binding site in brain (1988 Devane)
- Cloning cannabinoid I receptor (1990 Matsuda)
- Anandamide (1992 Devane)
- Cannabinoid II receptor (1993 Munro)
- 2-arachidonylglycerol [2-AG] (1995 Mechoulam)



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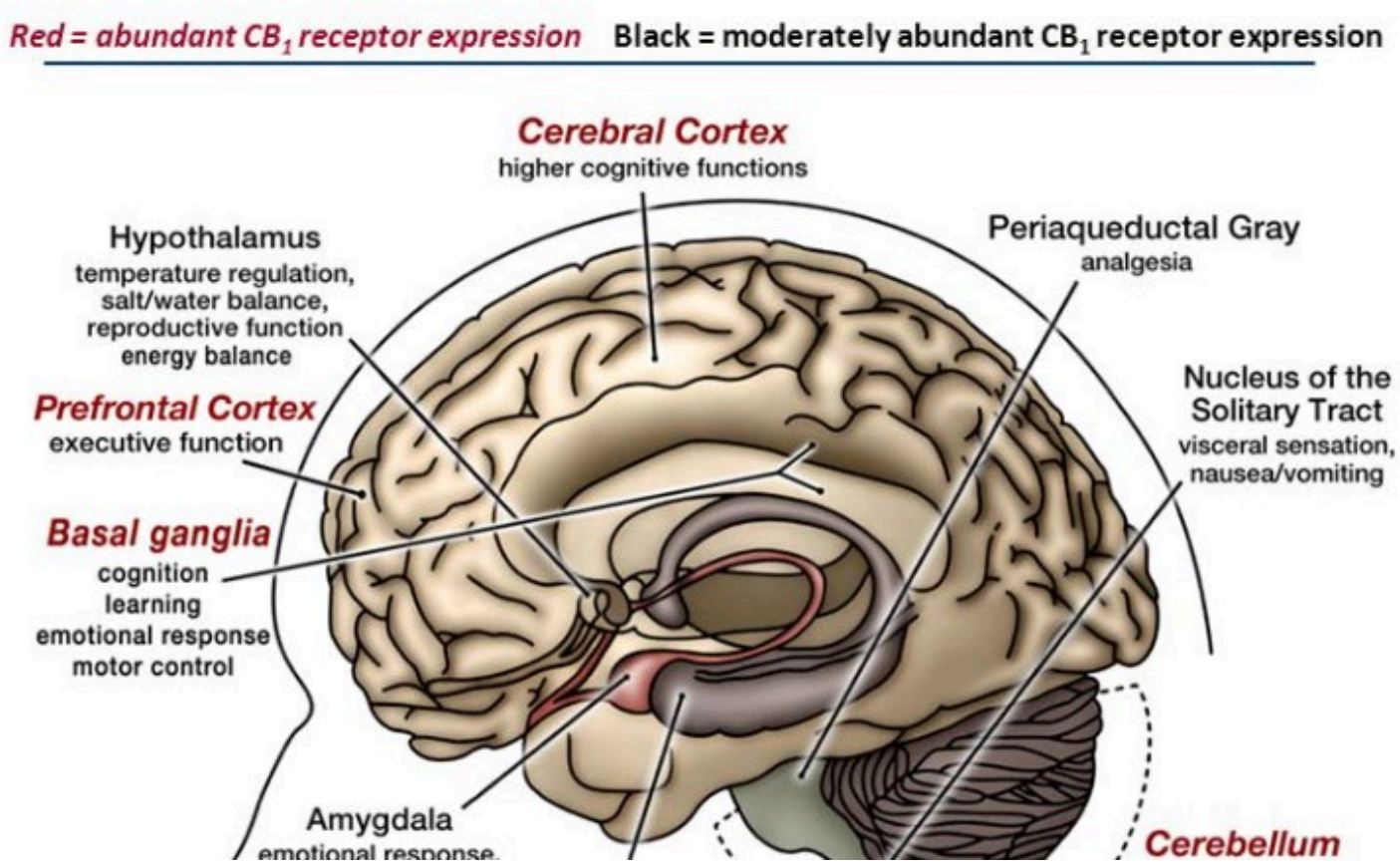

Endocannabinoid Receptor System – CB1R

- Mainly CNS: substantia nigra, basal ganglia, limbic system, hippocampus, cerebellum
- Limited receptors in: PNS, liver, thyroid, bone, uterus, testicles
- The most abundant G-protein coupled receptor in the body

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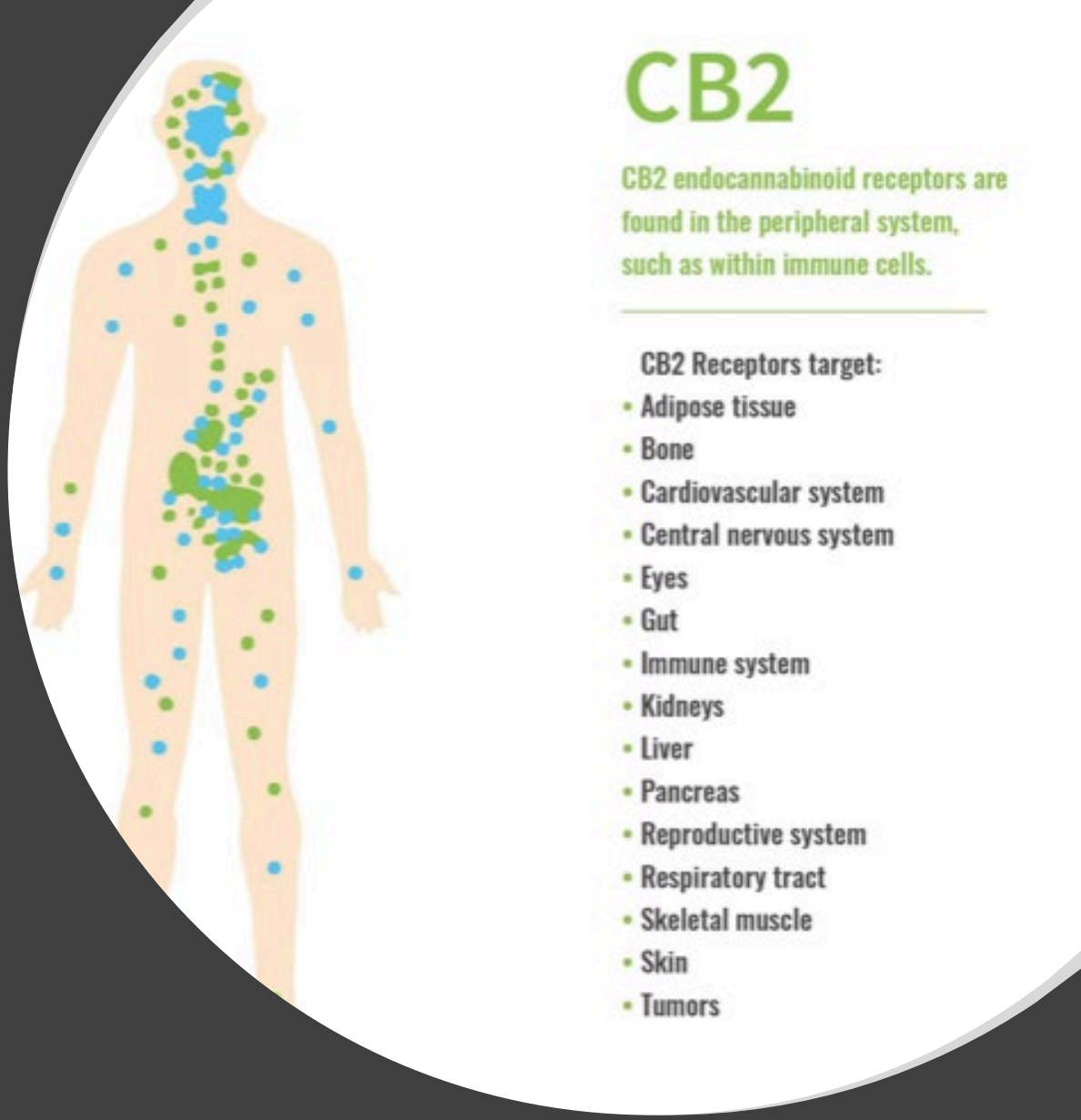
Endocannabinoid Receptor System – CB2R

- Mainly expressed in: immune cells, spleen, gastrointestinal tract.



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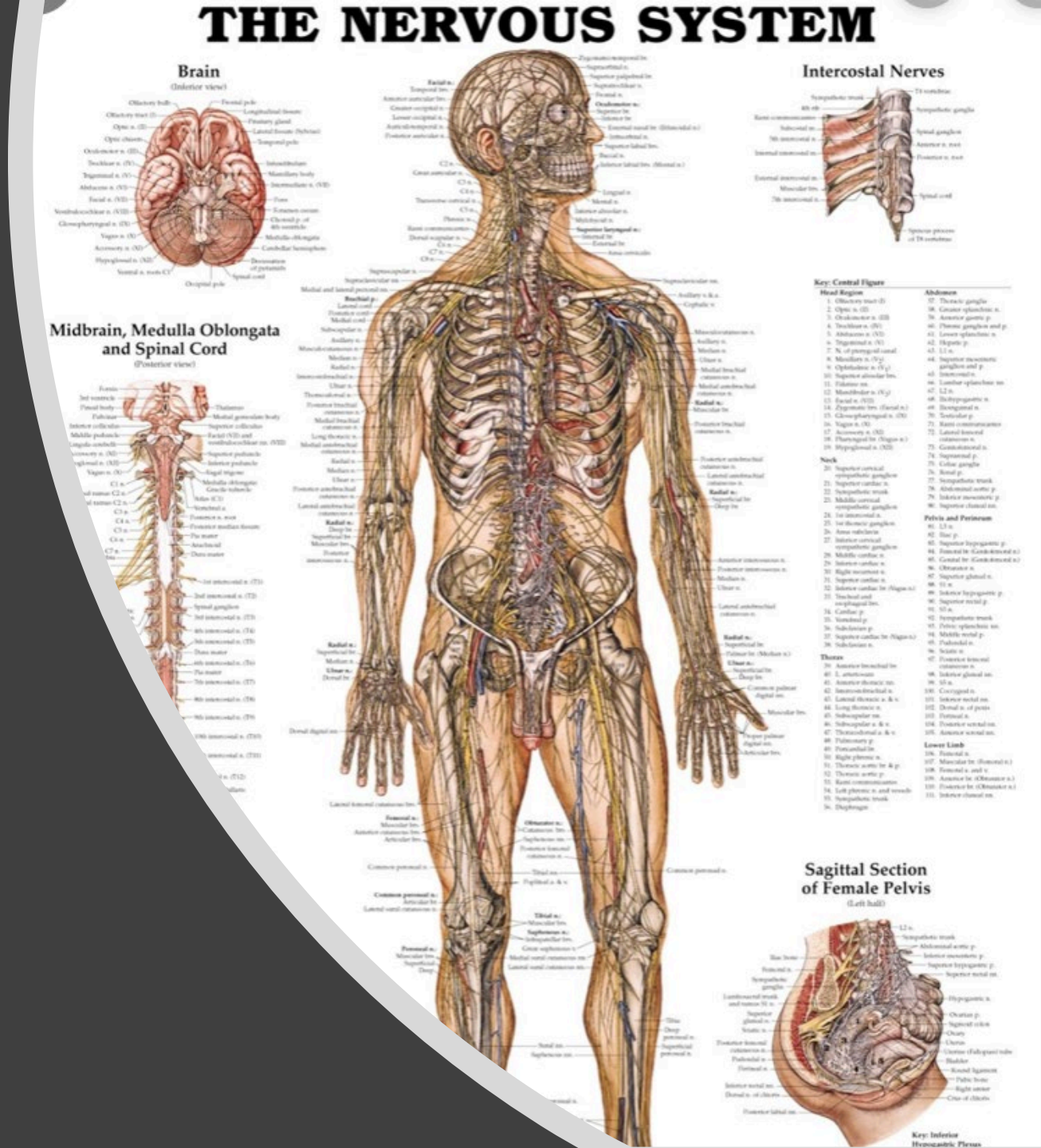
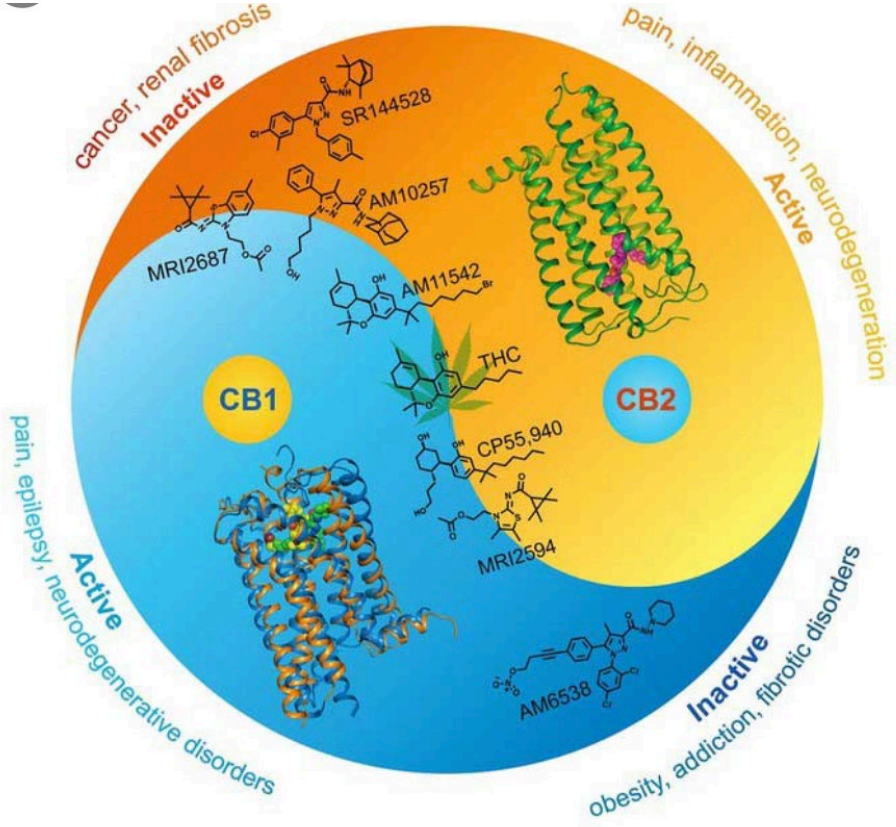
Endocannibinoid System

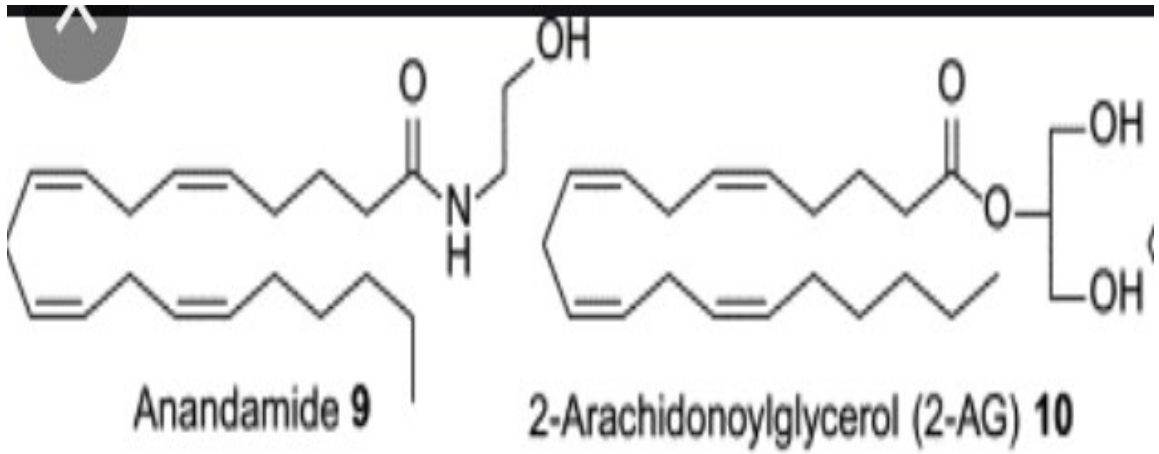
- Mediate inhibitory actions on all receptors, both excitatory and inhibitory: dopaminergic, GABA, glutaminergic, serotoninergic, acetylcholine, noradrenergic.

- MAINTAIN HOMEOSTASIS



Endocannabinoid System





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Cannabinoids Beyond the Endocannabinoid System

TRPV

- Transient Receptor Potential Cation Subfamily V (Vanilloid)
- In PNS, mediates pain perception
- In CNS, mediates thermoregulation

mTOR

- Mammalian Target of Rapamycin Signaling Pathway
- A serine/threonine protein kinase
- Complex 1: cell proliferation, motility, autophagy
- Complex 2: insulin receptor, insulin-like growth factor

Cannabinoids Beyond the Endocannabinoid System

PPAR

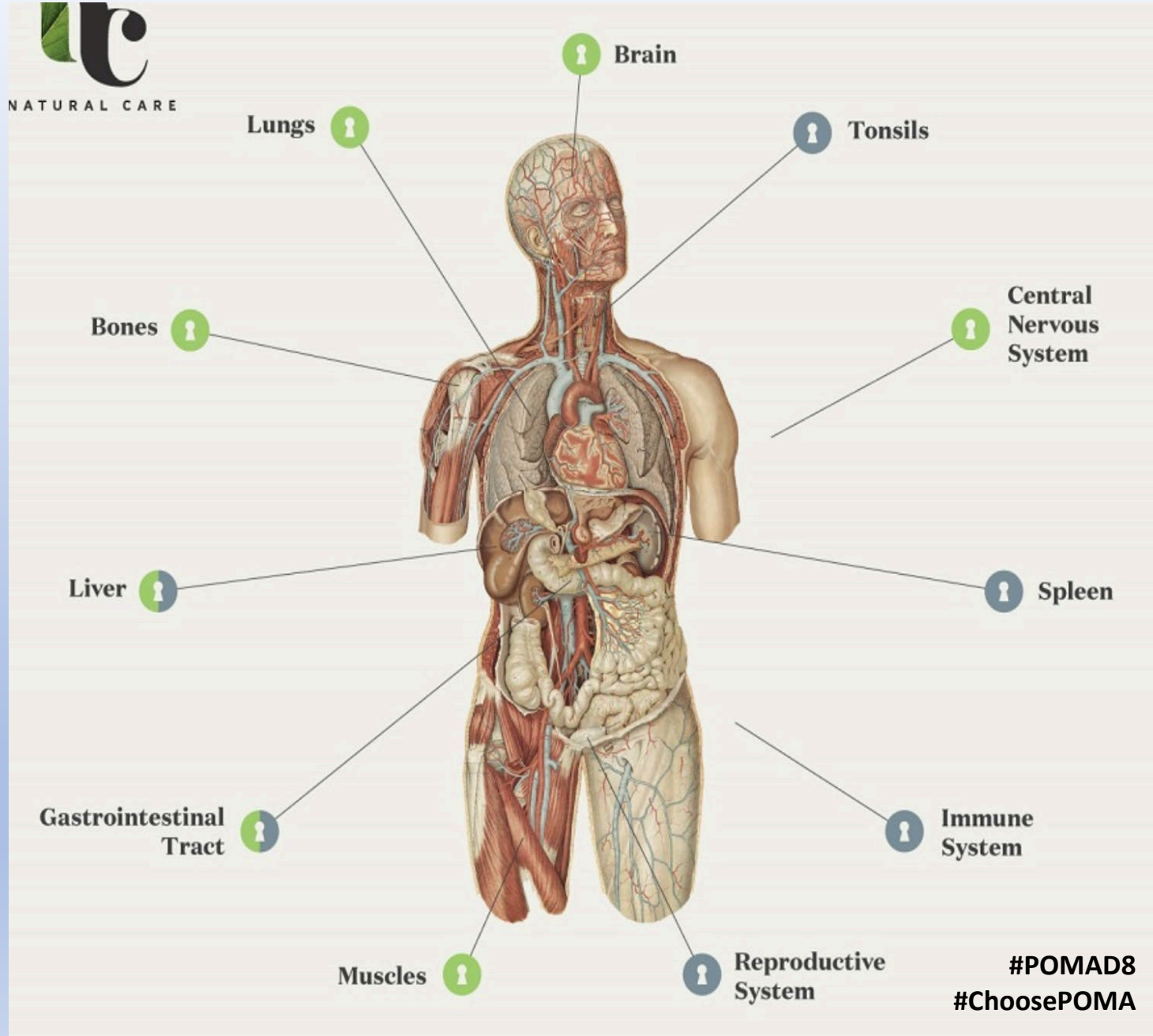
- PPARγ agonists decrease triglycerides and decrease glucose (glitazones)
- PPARα agonists lower triglycerides
- Peroxisome Proliferator-Activated Receptor
- Nuclear receptor protein that regulates gene expression, cell differentiation, metabolism, tumorigenesis

5-HT

- Serotonin Receptor
- Six of the seven sub-types are G-protein coupled
- Both excitatory and inhibitory effects on both neurotransmitters and hormones
- Throughout central and peripheral nervous system

AREAS OF RESEARCH

- IBS
- NEUROPROTECTION
- PAIN
- ANXIETY
- OBESITY
- CARDIAC
- ENDOCANNABINOID DEFICIENCY



Orthopedics and Marijuana

- JLongTermEffMedImplants.2018 (28)2: 125-130. Review of 2,718,023 total knee arthroplasty: 12.8% revision in cannabis users vs. 9.0% revision in non-cannabis users ($p<0.001$). Time to revision was decreased in cannabis users ($p<0.001$). Infection 34% non-cannabis vs. 37% cannabis users.

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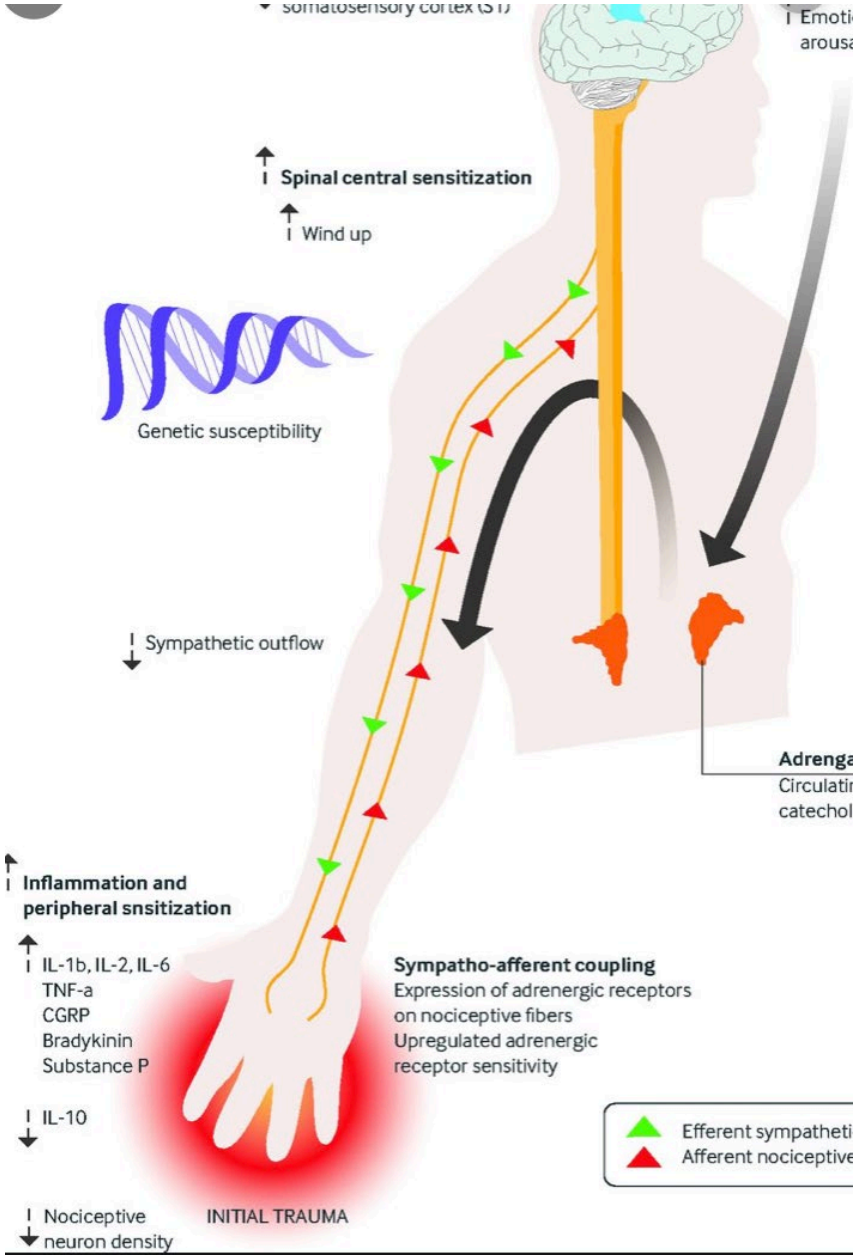
Pain Syndromes



- **8% of U.S. population has neuropathic pain**
- **Hyperalgesia vs. Allodynia**
- **Opioids vs. NSAIDs vs. Na^+ channel blockers vs. CBD vs. THC vs. multidisciplinary approach**

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CBD for Pain

- DeGregorio, et al. J Pain 2019 Jan; 160(1): 136-150.
- Animal model
- CBD 0.1mg/kg decreased 5-HT activity in dorsal raphe nucleus

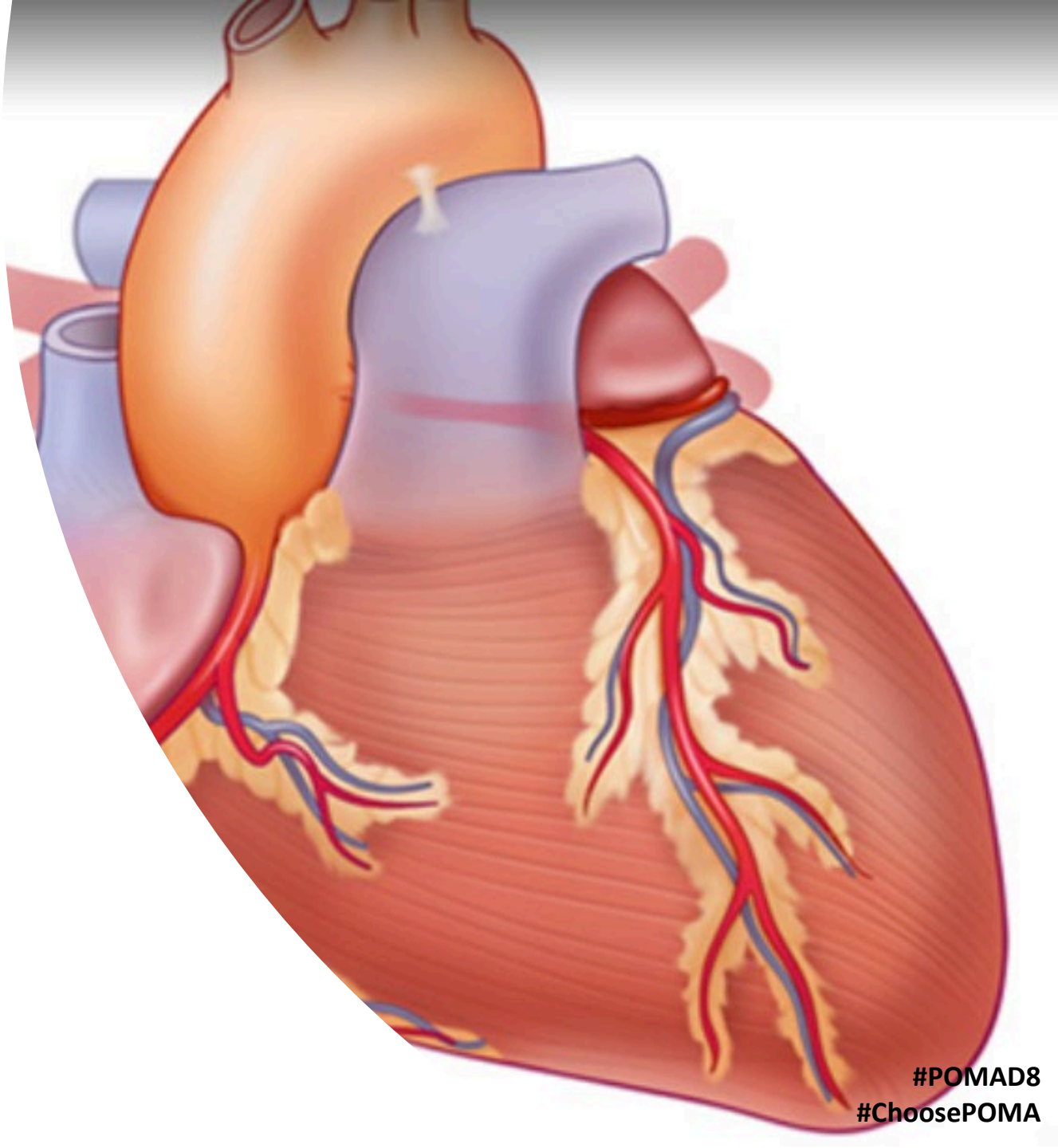
- Medical Marijuana for Chronic Pain. N Engl J Med 2018: 379; 16: 1575-1577.

- Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain 2015; 16(7): 616-627

- Double blind, placebo-controlled crossover study
- 1% p=0.03
- 4% p=0.04
- 7% p<0.001

Cannabinoids and your Heart

- Cannabinoid-sensitive receptors in cardiac physiology and ischaemia. Biochim Biophys Acta Mol Cell Res. 2019 Mar16pii: S0167-4889(18)30338-0.
- In cardiac ischemia, CB1 agonists aggravate inflammation; CB2 agonist mitigate inflammation.
- Increased risk of M.I. acutely with MJ use, but chronic use decreases risk.



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THCA-A and Obesity

- **Biochemical Pharmacology doi:10.1016/j.bcp.2019113693**
- **THCA-A as selective PPARγ modulator, lowers adipogenic activity more than rosiglitazone**
- **Ameliorates glucose intolerance**
- **Prevents hepatic steatosis and adipogenesis**

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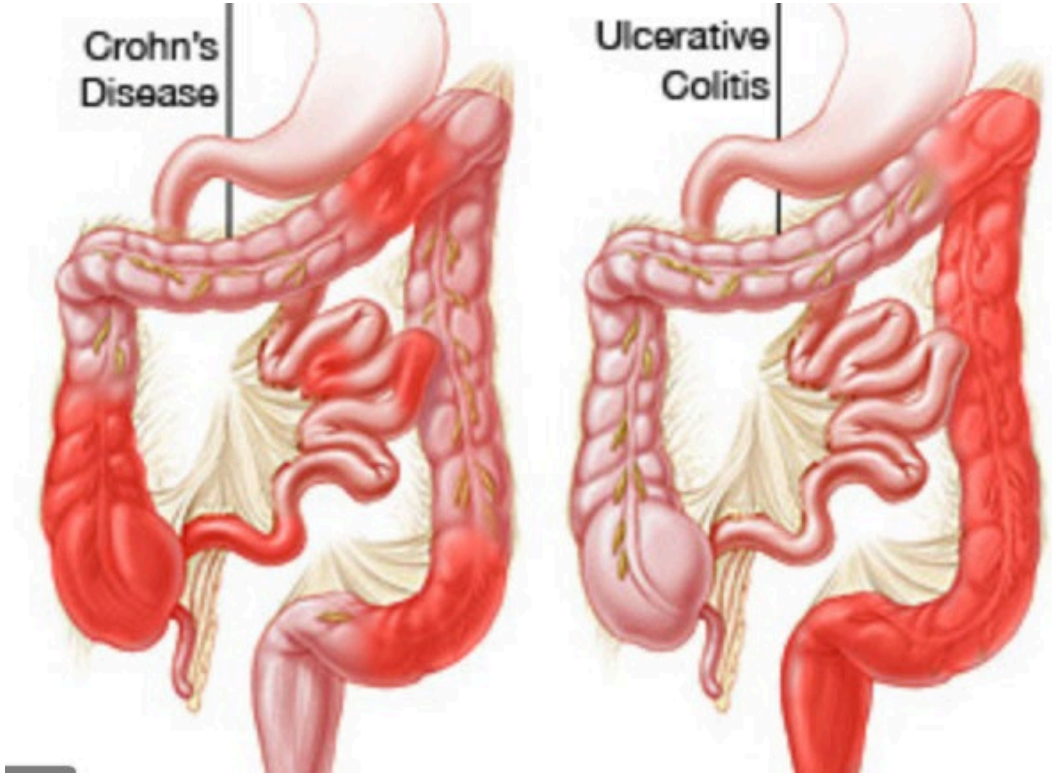
Cannabinoids and IBS

- Enteric glial cells mediate acute/chronic inflammation. CBD reduced TNF-α, caspase-3, S100B, and iNOS, partly thru PPARγ.
- Kafil TS, et al: Cannabis in Crohn's & UC: Cochrane Review(2019) – NO EFFECT.
- Couch DG, et al: Cannabinoids in colitis(2019) – POSITIVE EFFECT.



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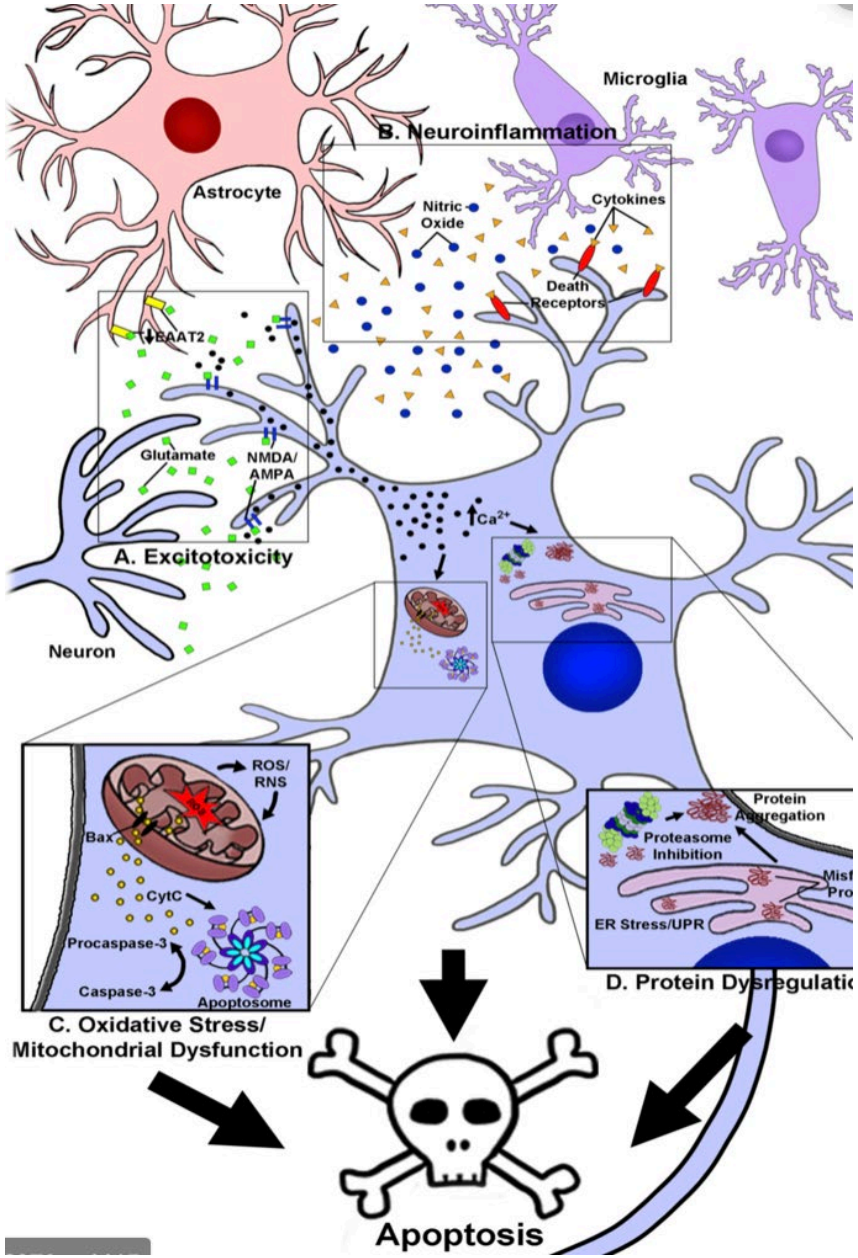
Neuroprotection and Cannabinoids



- **THCA attenuates microgliosis, astrogliosis and the upregulation of pro-inflammatory markers in animal model.**
- **Analogues (JWH133; HU210) considered for neurodegenerative diseases**
- **But, CBD in Parkinsons made tremors worse.**

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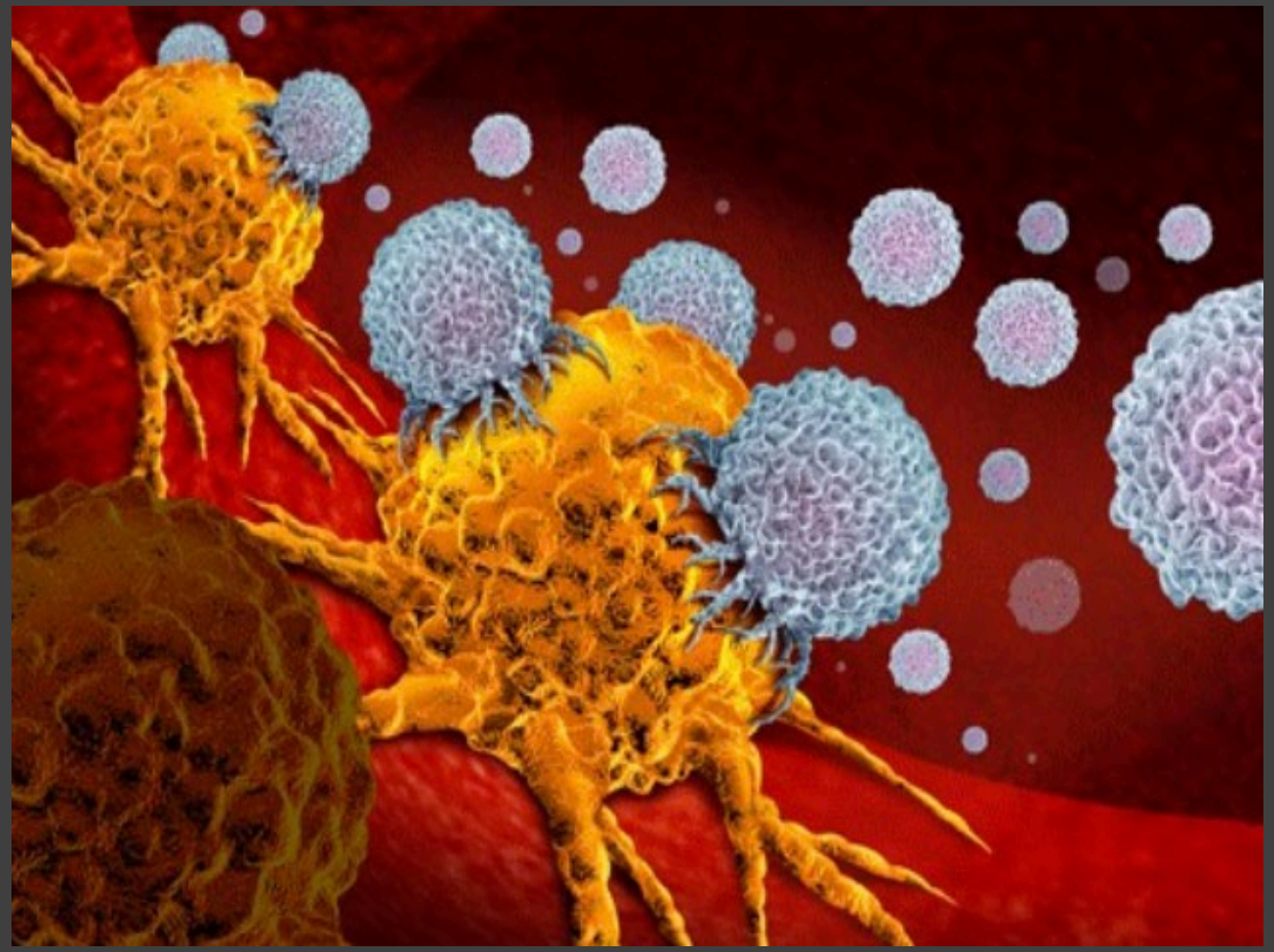
Cannabinoids and Cancer



- Endocannabinoids absolutely have effect in proliferation, invasiveness and metastasis of cancer.
- ? Increase vs. decrease ?
- Ramer R, et al: CBD is proapoptotic in lung cancer cell line by upregulating COX-2 and PPARγ
- Ghasemiesfe M: JAMA 2019. Chronic marijuana use increased risk of testicular cancers.

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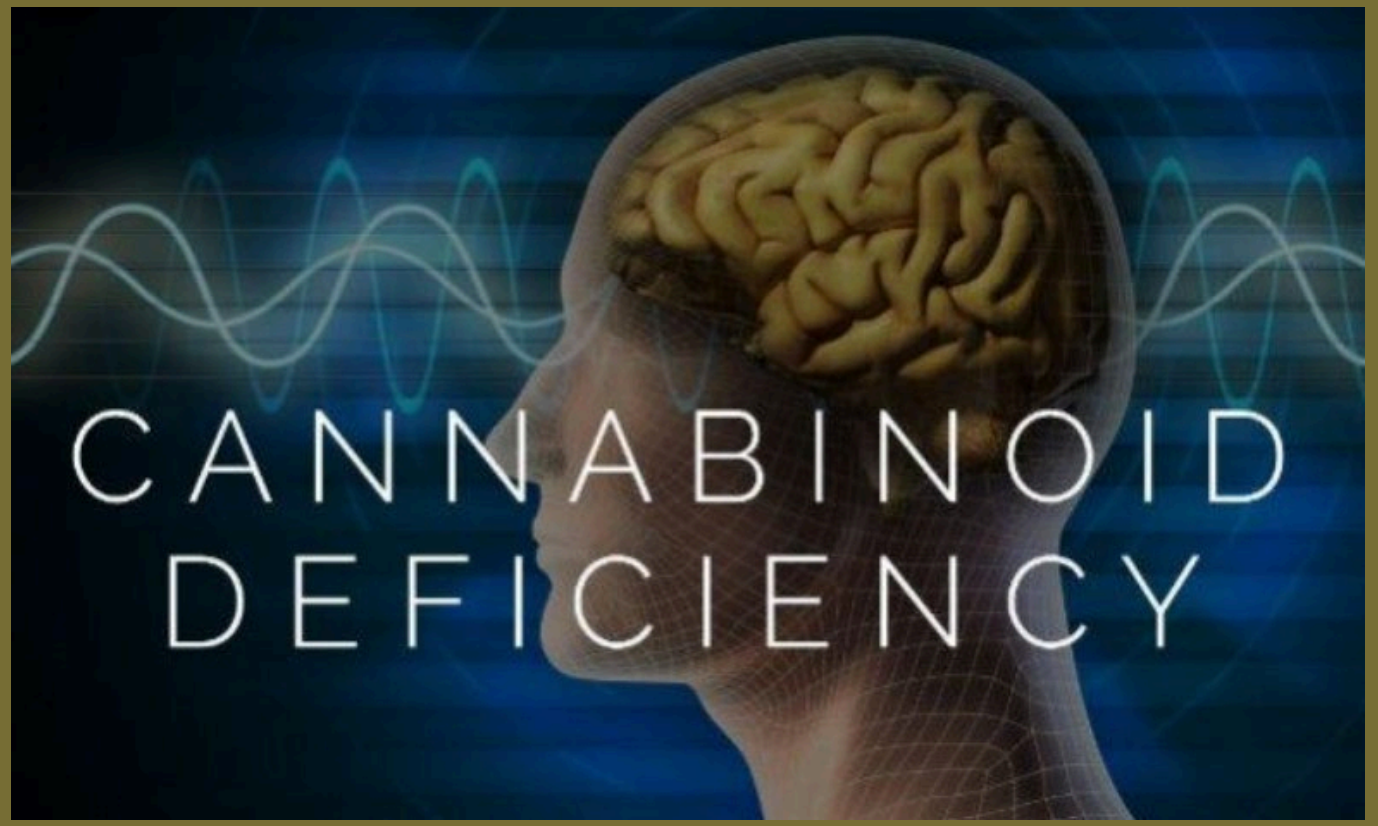
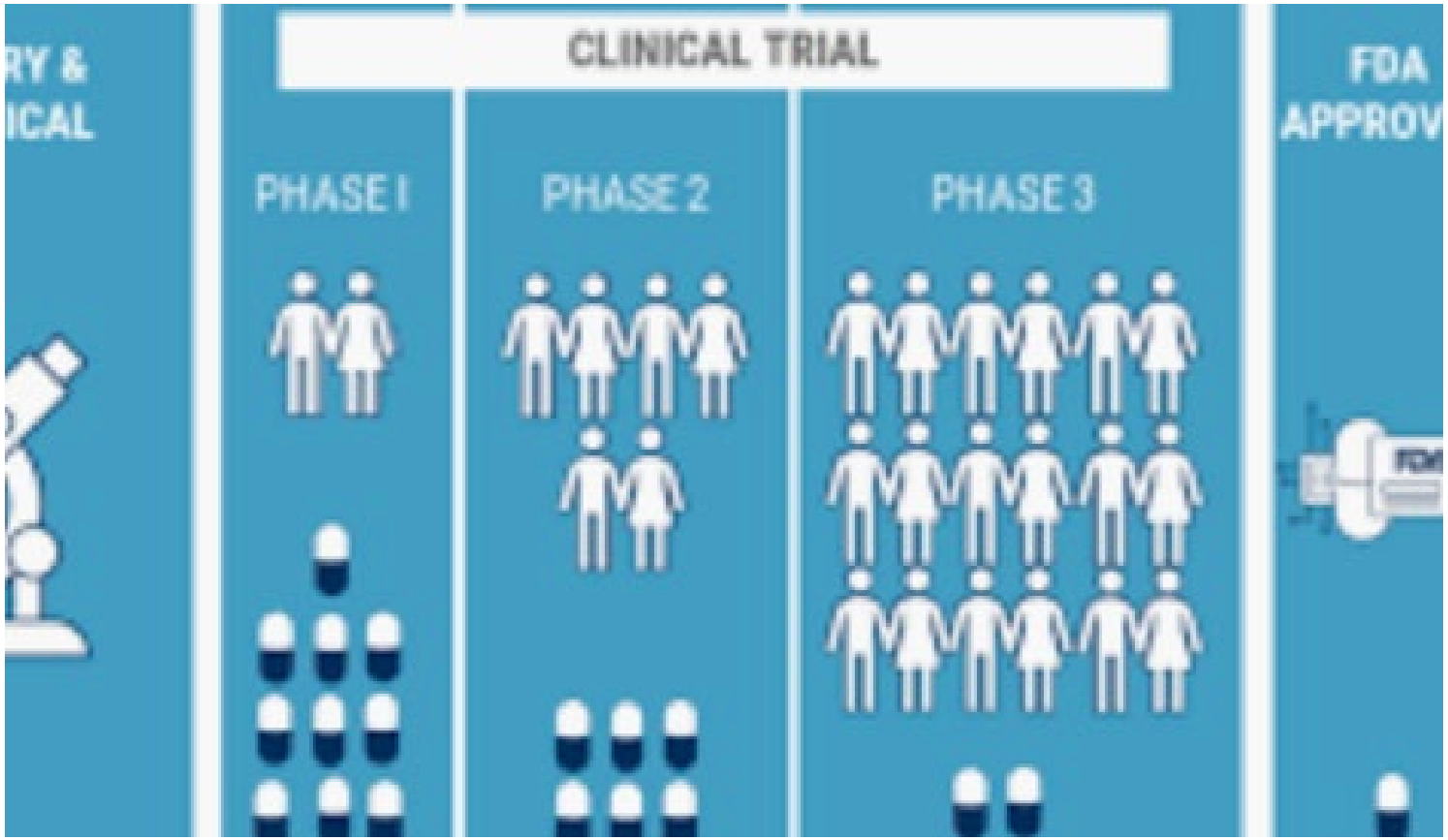
Clinical Endocannabinoid Deficiency



- Analogous to other deficiency syndromes: Parkinson's… Alzheimer's… Depression…
- Main players: migraine, IBS, fibromyalgia.
- See Article by Russo.

PATENTS

- CBD for graft vs. host disease
- CBD for rheumatoid arthritis, multiple sclerosis, and Crohns
- Systems, methods, & composition of blended cannabinoid beverages
- CBD wine
- Intranasal THC for Rx of acute seizures
- Topical cannabinoids for epidermolysis bullosa



CLINICAL TRIALS

- Pharmacokinetic and pharmaco- dynamics of CBD via inhalation and oral ingestion.
- CBD as a treatment for alcohol-use disorder comorbid with PTSD.
- CBD in patients with heart failure AHA/ACC Stages A-C
- CBD as an adjunct for Crohn’s disease

Clinical Trials

- CBD vs. olanzapine for treatment of schizophrenia
- CBD & THC in Multiple Sclerosis
- CBD for behavioral symptoms in Alzheimers dementia
- CBD in patients with multiple myeloma or glioblastoma or g.i. malignancies
- Safety & efficacy of CBD for grade I/II acute graft vs. host disease in allogenic stem cell transplant

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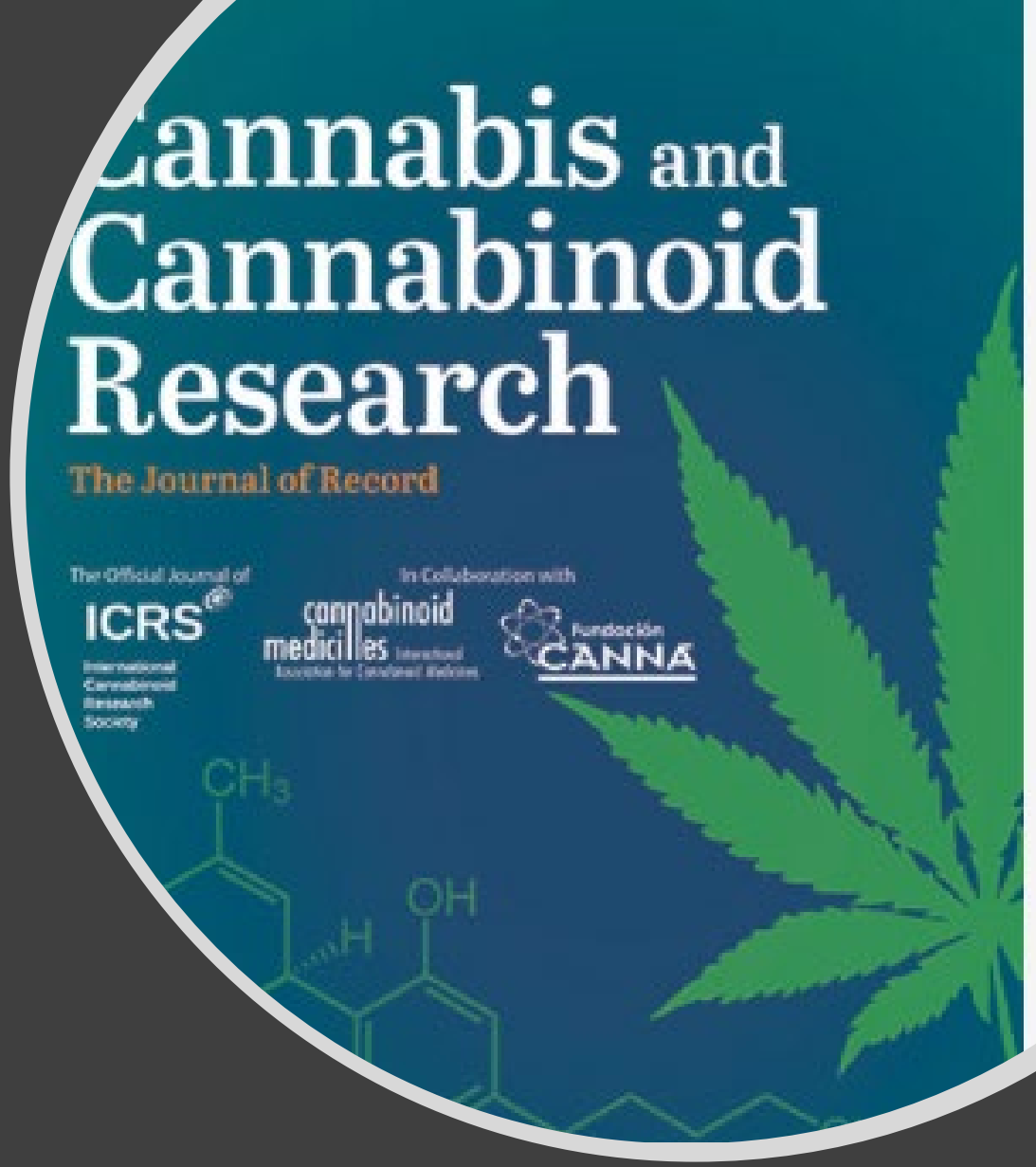

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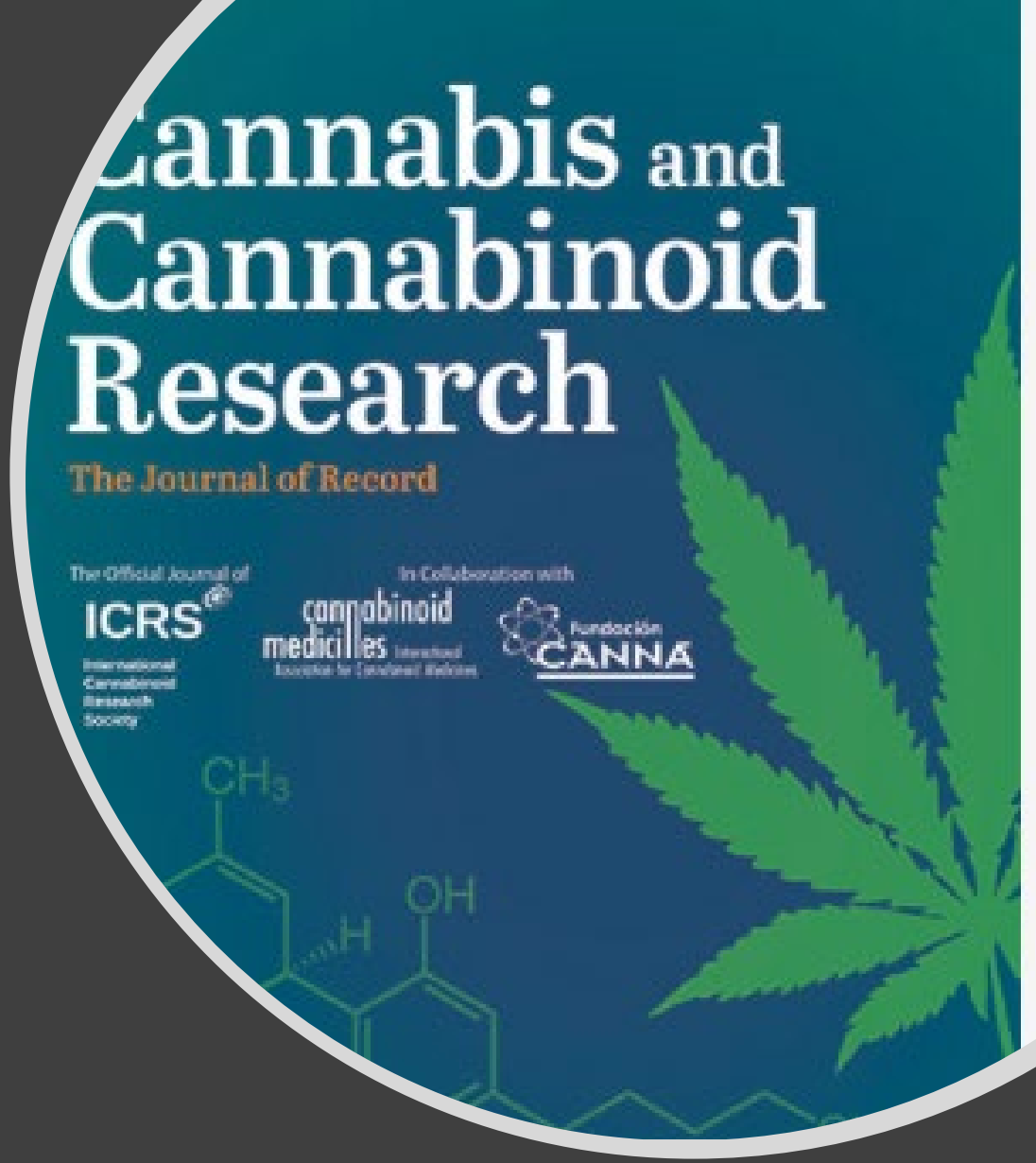

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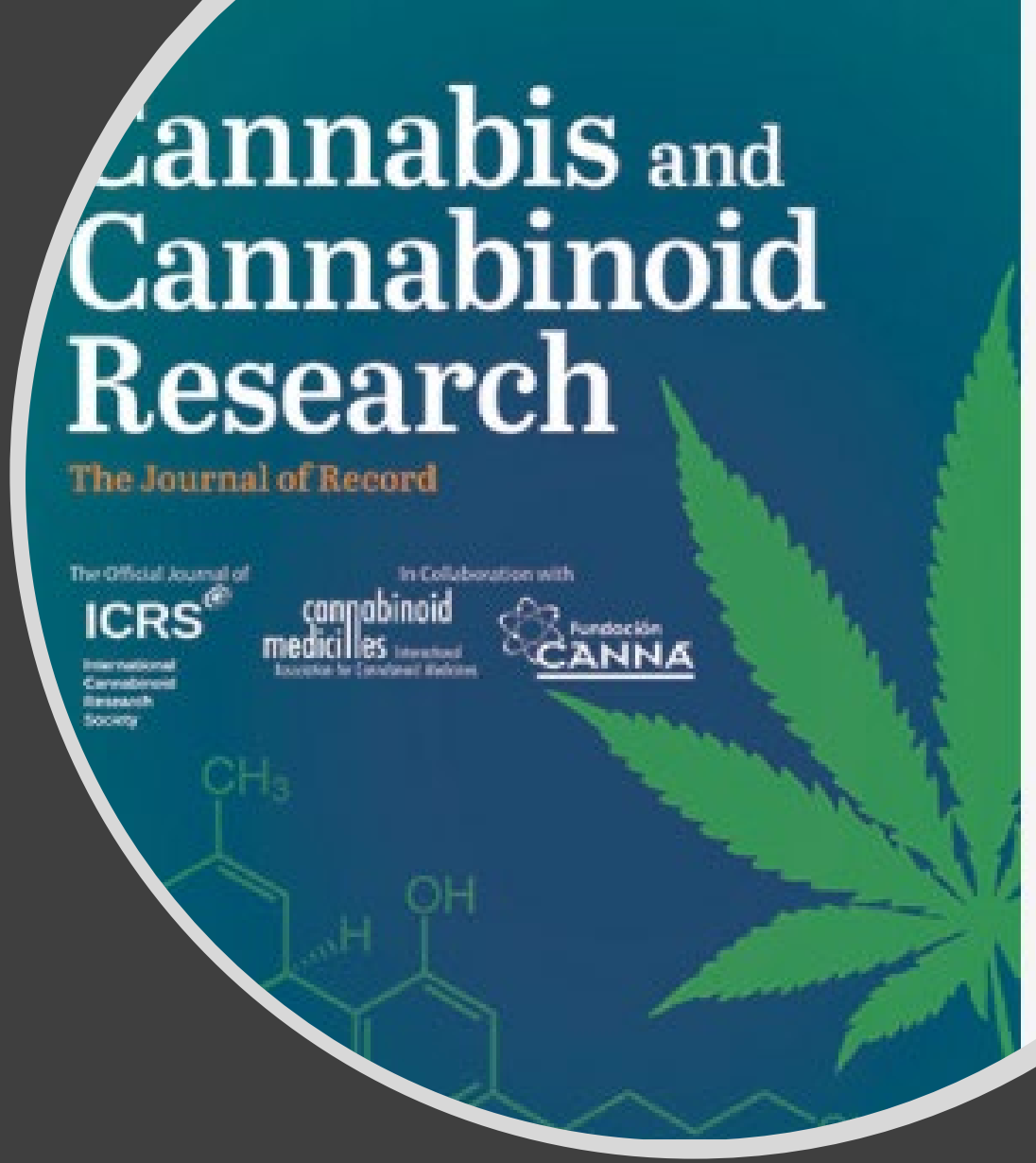

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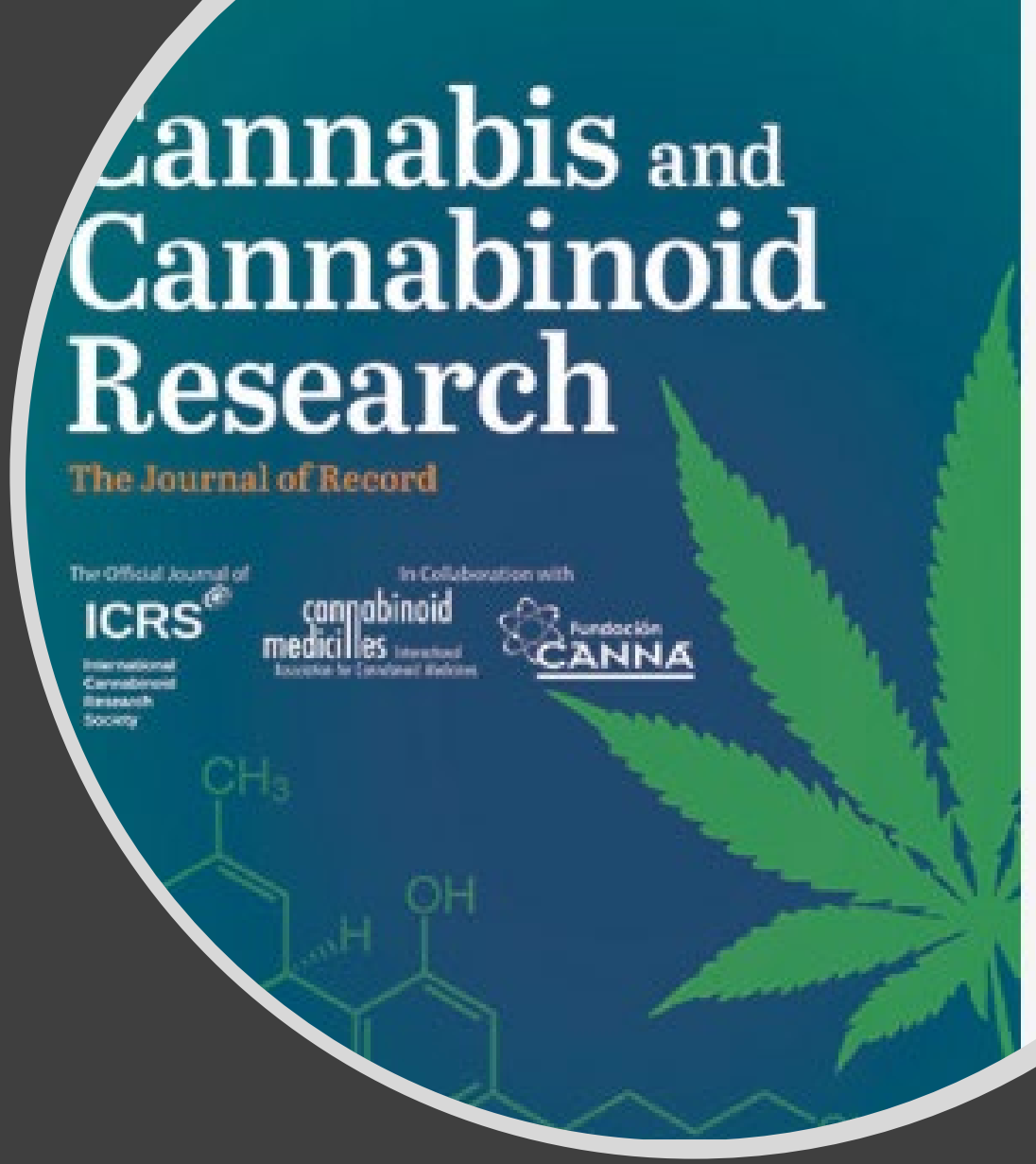

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