

# CANNABINOIDS: NOVEL MOLECULES WITH SIGNIFICANT CLINICAL UTILITY

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# How Did We Get Here?

- In November 2012 Tikun Olam, an Israeli medical cannabis facility, announced a new strain of the plant which has only CBD as an active ingredient, and **virtually no THC**, providing some of the medicinal benefits of cannabis without euphoria. The Researchers said the cannabis plant, enriched with CBD, “can be used for treating diseases like rheumatoid arthritis, colitis, liver inflammation, heart disease and diabetes.” **Cannabis CBD like in this article is legally derived from the hemp plant.**
- CBD is the major non-psychoactive component of Cannabis Sativa (Hemp). Hemp plants are selectively developed and grown to contain high amounts of CBD and very low amounts of the psychoactive component THC found in marijuana. **A few CBD oil manufacturers further purify their products to contain high amounts of CBD and no THC.**

# 2014 Farm Bill

All of the products manufactured and marketed by **Full Spectrum Nutrition, LLC** use Colorado industrial hemp oil derived extracts. “Industrial Hemp” is legally defined in Federal legislation as products derived from *Cannabis sativa L* which contain less than 0.3% THC on a dry weight basis.

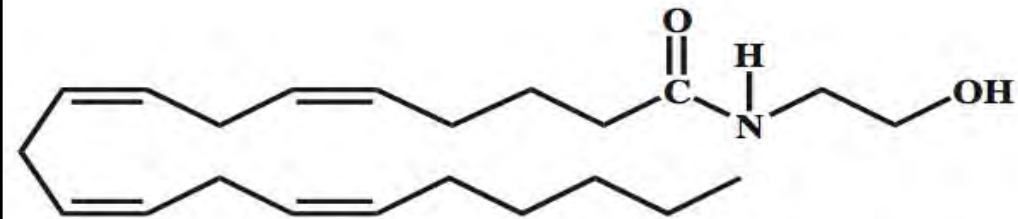
With the passage of the **2014 Farm Bill**, the United States Congress differentiated industrial hemp from marijuana plants. Section 7606 of the 2014 Farm Bill authorized the growth, cultivation and marketing of industrial hemp under agricultural pilot programs in states that have legalized such activities. States with permitting agricultural programs may authorize, upon the granting of an applicant’s application, the issuance of a State license to lawfully participate under the 2014 Farm Bill’s hemp program. The suppliers of our CBD materials are certainly licensed by the State of Colorado, and fully compliant with regulations to lawfully participate in the provisions provided by the 2014 Farm Bill.

There is the potential for confusion about the legality of CBD after the U.S. Drug Enforcement Administration (DEA) published a rule about CBD on December 13, 2016. In its announcement, the DEA restated its rule that *all cannabis extracts*, which includes CBD, are considered Schedule 1 substances. The agency issued this clarification to ensure American laws conformed with the treaties established by the United Nations to govern controlled substances. The rule was instantly challenged in Federal court by hemp and CBD oil producers from across the United States.

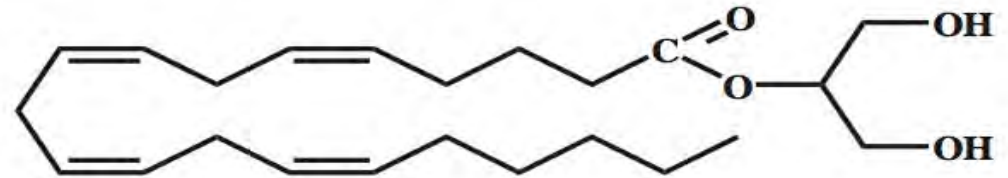
# Terminology

- Active Ingredient
- Zero THC
- Cannabidiol
- Isolate
- PCR – Phytocannabinoid-Rich
- Hemp Oil Extract
- “Recommendation” vs. “Prescribed”
- Full Spectrum

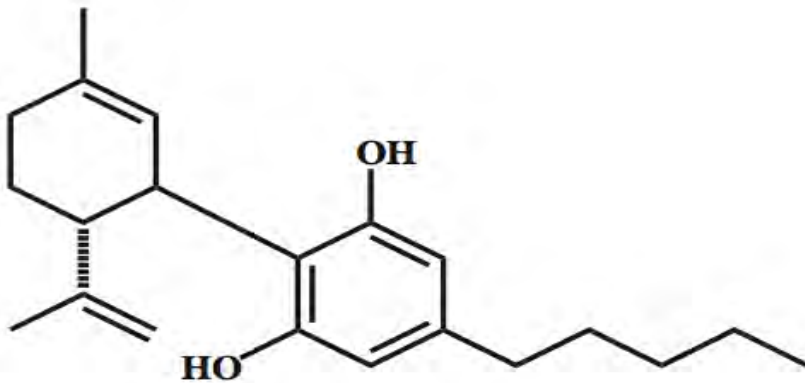
## Endocannabinoids



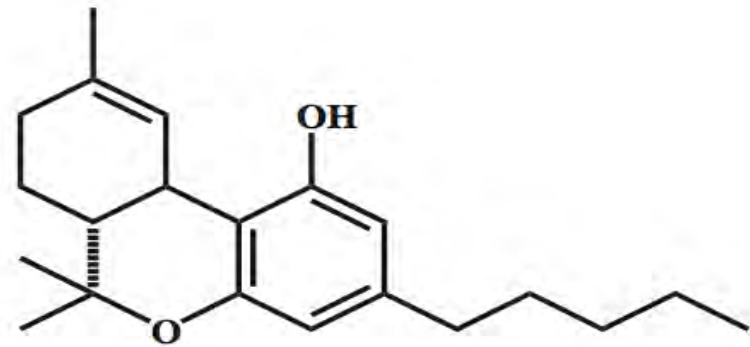
Arachidonoyl ethanolamide (anandamide)(AEA)



2-arachidonoyl glycerol (2-AG)

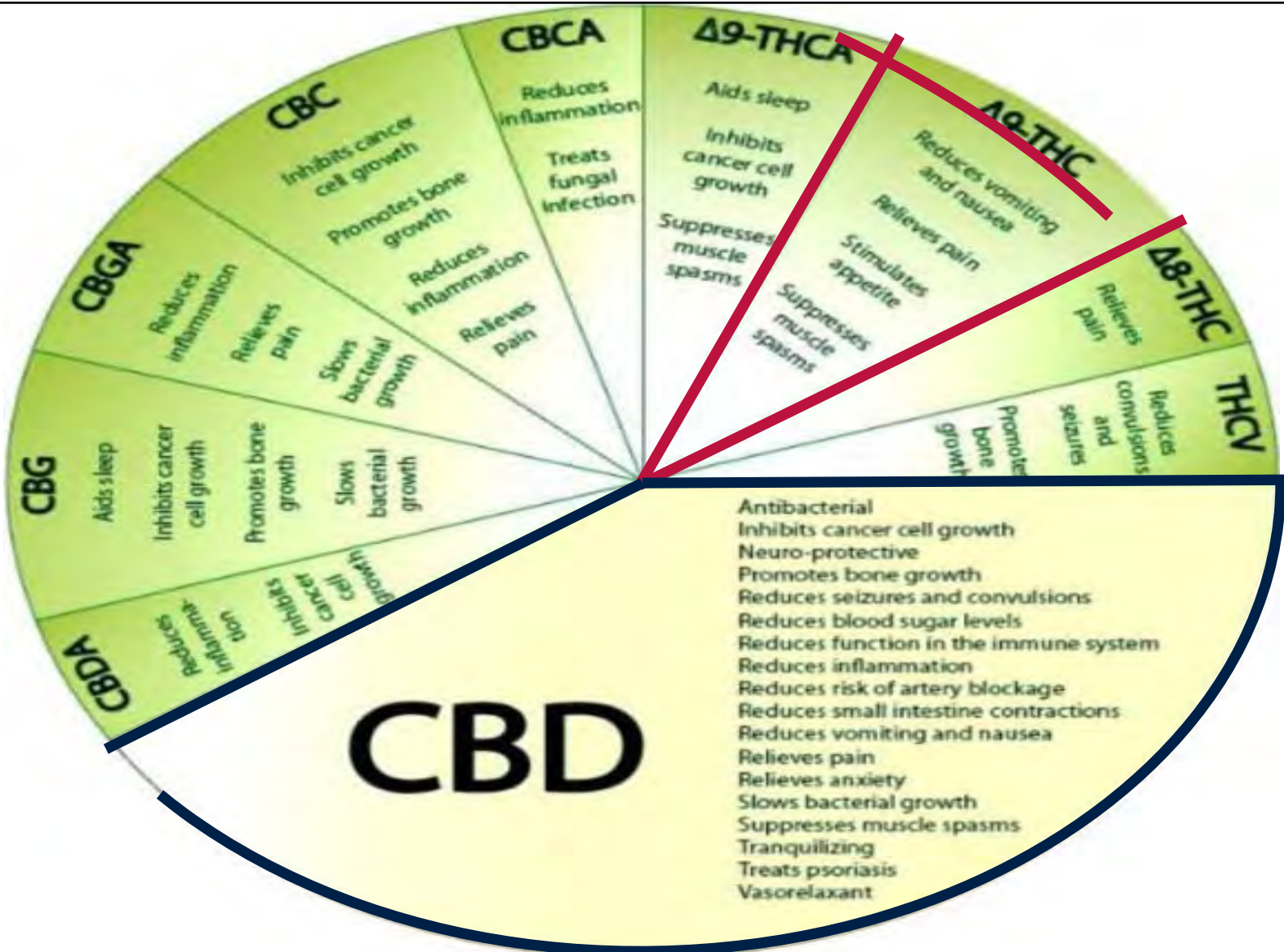


Cannabidiol (CBD)



$\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC)

## Phytocannabinoids





# Full Spectrum & Active Ingredient

- CBD – Cannabidiol
  - A major phytocannabinoid, accounting for as much as 85% of the plant's extract
- CBC – Cannabichromene
  - Anti-inflammatory & anti-fungal effects have been seen
- CBG – Cannabigerol
  - The parent molecule from which many other cannabinoids are made
- CBDV – Cannabidivarin
  - A homolog of CBD that has been reported to have powerful anti-convulsive effects
- CBN – Cannabinol
  - Sleep & Appetite regulation
- Terpenes
  - Wide spectrum of non-psychoactive molecules that are known to act on neural receptors and neurotransmitters, enhance norepinephrine activity, and potentially increase dopamine activity.

Enhanced Clinical Nutrition

# What do these men have in common?

- **Aiden Hampson**, a neuropharmacologist at the Natl Inst for Mental Health (NIMH). Now Health Science Administrator, Natl Inst of Drug Abuse (NIDA), Medications Research Grants Branch
- **Julius Axelrod** (1912-2004), Professor Emeritus, NIH, pharmacologist and neuroscientist who shared the 1970 Nobel Prize in Physiology or Medicine for his discovery of the actions of neurotransmitters in regulating the metabolism of the nervous system
- **Maurizio Grimaldi**, professor of neurology/ neuropsychopharmacology and toxicology, NIMH. Now with Natl Inst on Aging, Scientific Review Branch



(1) **United States Patent**  
**Hampson et al.**

(10) **Patent No.:** **US 6,630,507 B1**  
(45) **Date of Patent:** **Oct. 7, 2003**

(54) **CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS**

(75) Inventors: **Aidan J. Hampson**, Irvine, CA (US);  
**Julius Axelrod**, Rockville, MD (US);  
**Maurizio Grimaldi**, Bethesda, MD (US)

(73) Assignee: **The United States of America as represented by the Department of Health and Human Services**, Washington, DC (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/674,028**

(22) PCT Filed: **Apr. 21, 1999**

(86) PCT No.: **PCT/US99/08769**

§ 371 (c)(1),  
(2), (4) Date: **Feb. 2, 2001**

(87) PCT Pub. No.: **WO99/53917**

PCT Pub. Date: **Oct. 28, 1999**

(57) **ABSTRACT**

Cannabinoids have been found to have antioxidant properties, unrelated to NMDA receptor antagonism. This new found property makes cannabinoids useful in the treatment and prophylaxis of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases. The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia. Nonpsychoactive cannabinoids, such as cannabidoil, are particularly advantageous to use because they avoid toxicity that is encountered with psychoactive cannabinoids at high doses useful in the method of the present invention. A particular disclosed class of cannabinoids useful as neuroprotective antioxidants is formula (I) wherein the R group is independently selected from the group consisting of H, CH<sub>3</sub>, and COCH<sub>3</sub>.

## **Cannabidiol and (–) $\Delta^9$ -tetrahydrocannabinol are neuroprotective antioxidants**

[A. J. Hampson](#),<sup>\*†</sup> [M. Grimaldi](#),<sup>‡</sup> [J. Axelrod](#),<sup>\*</sup> and [D. Wink](#)<sup>§</sup>

**This study reports that CBD and other cannabinoids such as THC are potent antioxidants that protect neurons from glutamate-induced death without cannabinoid receptor activation..... nonpsychoactive CBD was found to prevent both glutamate neurotoxicity and ROS-induced cell death.**

# History of Cannabis Suggests Safety

- 1850-1942 included in US Pharmacopeia as treatment for neuralgia, alcoholism, opiate addiction, convulsive disorders, several infectious diseases, insanity, among others
- Promoted as analgesic, sedative, antispasmodic, anticonvulsant, and anti-inflammatory
- Manufactured by Eli Lilly, Wyeth Park-Davis, Sharp & Dohme, and others
- 1937: AMA opposes Tax Act and supports research



# Cannabis Americana



## AS ACTIVE AS INDIAN CANNABIS

We are marketing a reliable fluid extract of *Cannabis Sativa* from American-grown drug. It has been thoroughly tested by experienced clinicians and pronounced fully equal to the fluid extract obtained from the best Indian Cannabis.

Fluid Extract Cannabis Americana (P. D. & Co.) is physiologically standardized. Practitioners may specify it with perfect assurance of its activity and uniformity. We market it at a price considerably lower than that asked for fluid extract Cannabis Indica.

*Supplied in pint, 1/2-pint and 5-pint bottles.*

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HOME OFFICES AND LABORATORIES, DETROIT, MICH.



**CANNABIS INDICA**  
(Catalogue No. 1716)  
physiologically; strength is 25 per cent of  
of the U. S. P. solid extract  
DOSE— $\frac{2}{3}$  grain (.043 Gm.)

FROM THE LABORATORY OF  
**THE W. M. S. MERRELL COMPANY**  
CINCINNATI, U.S.A.



One-Fourth Ounce—Solid Extract  
**CANNABIS AMERICANA**  
(*Cannabis sativa*—American grown)  
PHYSIOLOGICALLY TESTED  
DOSE—1-5 to 1 grain

**ELI LILLY & CO.**  
INDIANAPOLIS  
U. S. A.

**ONE-FOURTH POUND—SOLID EXTRACT**  
**CANNABIS AMERICANA**  
PHYSIOLOGICALLY TESTED  
(*Cannabis sativa*—American Grown)  
Analgesic, Hypnotic, Antispasmodic and powerful Narcotic  
DOSE—1-5 to 1 grain

OCT 11 1913 *Lilly*

**ELI LILLY & CO., INDIANAPOLIS, U. S. A.**  
Guaranteed by Eli Lilly & Co., under Food and  
Drugs Act, June 30, 1906. Guaranty No. 87.



# We All Have Cannabinoid Receptors

The cannabinoid receptors are further divided into 2 main subtypes, known as cb1 and cb2.



**CB1** is found mostly in the brain.

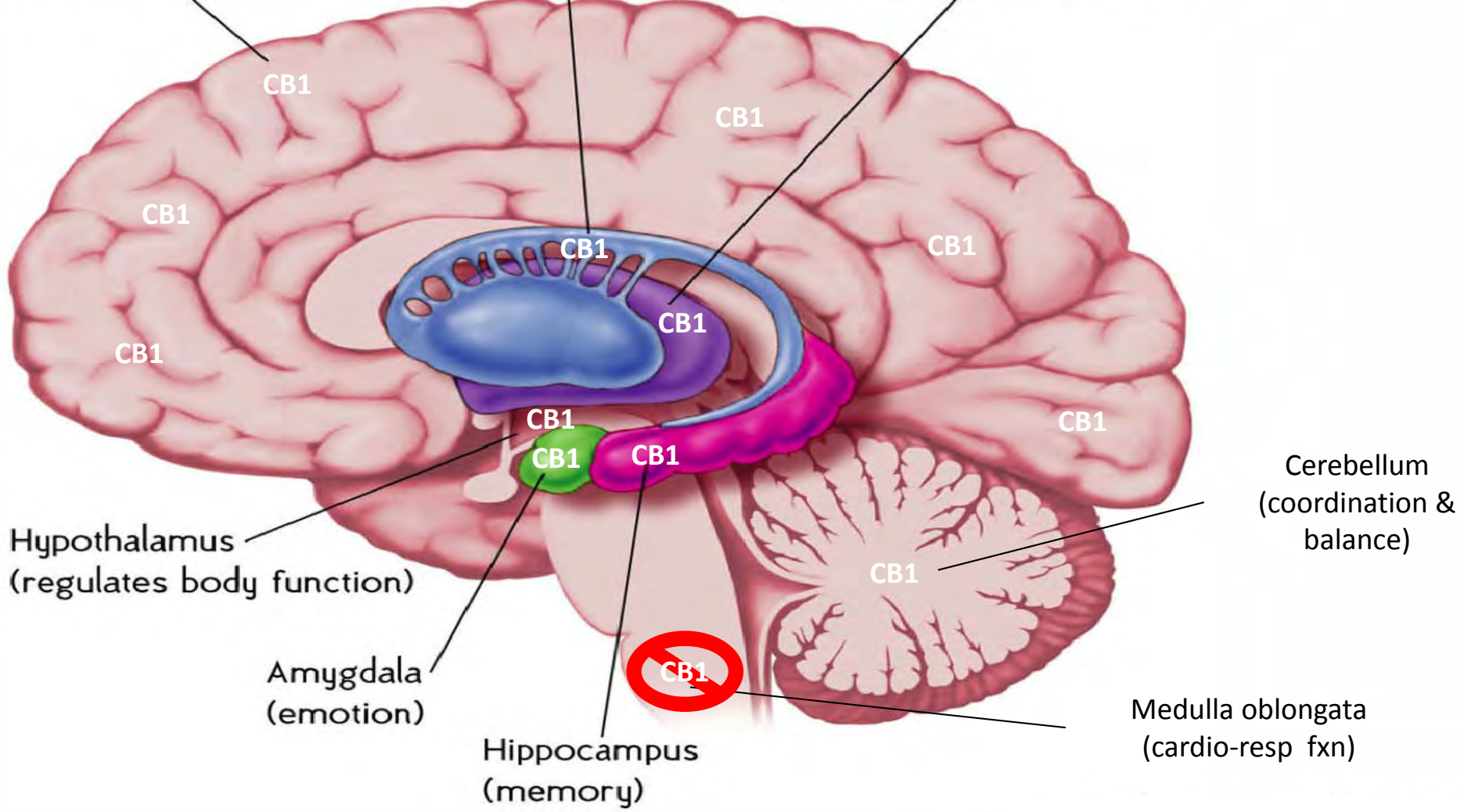


**CB2** receptors are mostly found within the immune system.

Cerebral cortex  
(thought, planning)

Basal ganglia  
(movement)

Thalamus  
(gateway to cortex)



CB1

CB1

CB1

CB1

CB1

CB1

CB1

CB1

CB1

Cerebellum  
(coordination & balance)

Hypothalamus  
(regulates body function)

Amygdala  
(emotion)

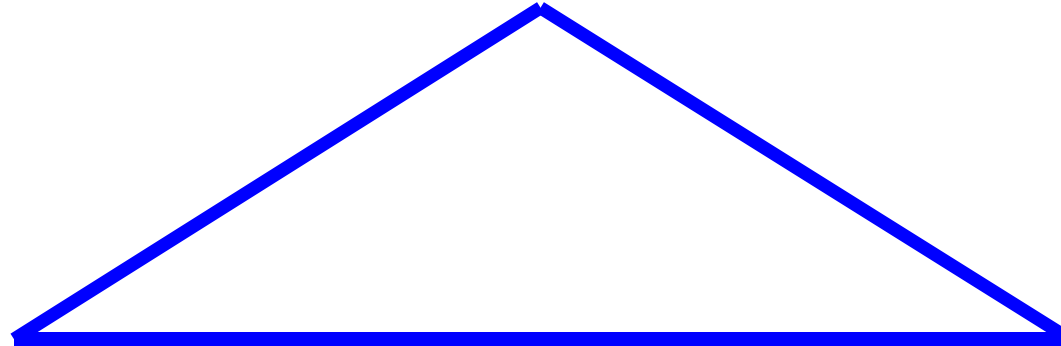
Hippocampus  
(memory)

Medulla oblongata  
(cardio-resp fxn)

~~CB1~~

# Endocannabinoid System (ECS) Triad

**Cannabinoid Receptors**  
CB1, CB2, TRPV1, 5-HT1A



**Endogenous  
Cannabinoids**  
[Anandamide (AEA)  
2-arachidonoylglycerol (2-AG)]

**Regulatory Metabolic/  
Catabolic Enzymes**  
[fatty acid amide hydrolase (FAAH),  
monoacylglycerol lipase (MAGL), and others]



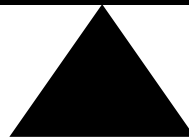
# Balanced Effects of Endocannabinoids

Ideally, if the ECS is functioning normally, a person might enjoy a normal mental state, without pain, have good digestive function, etc.

- Migraines
- Chronic pain
- Fibromyalgia
- IBS
- Depression

- PTSD

*Clinical  
Endocannabinoid  
Deficiency*



- **Metabolic syndrome**
- **Obesity & over-eating**
- **Increased inflammation**
- **Insulin resistance/diabetes**
- **Mental health instability**

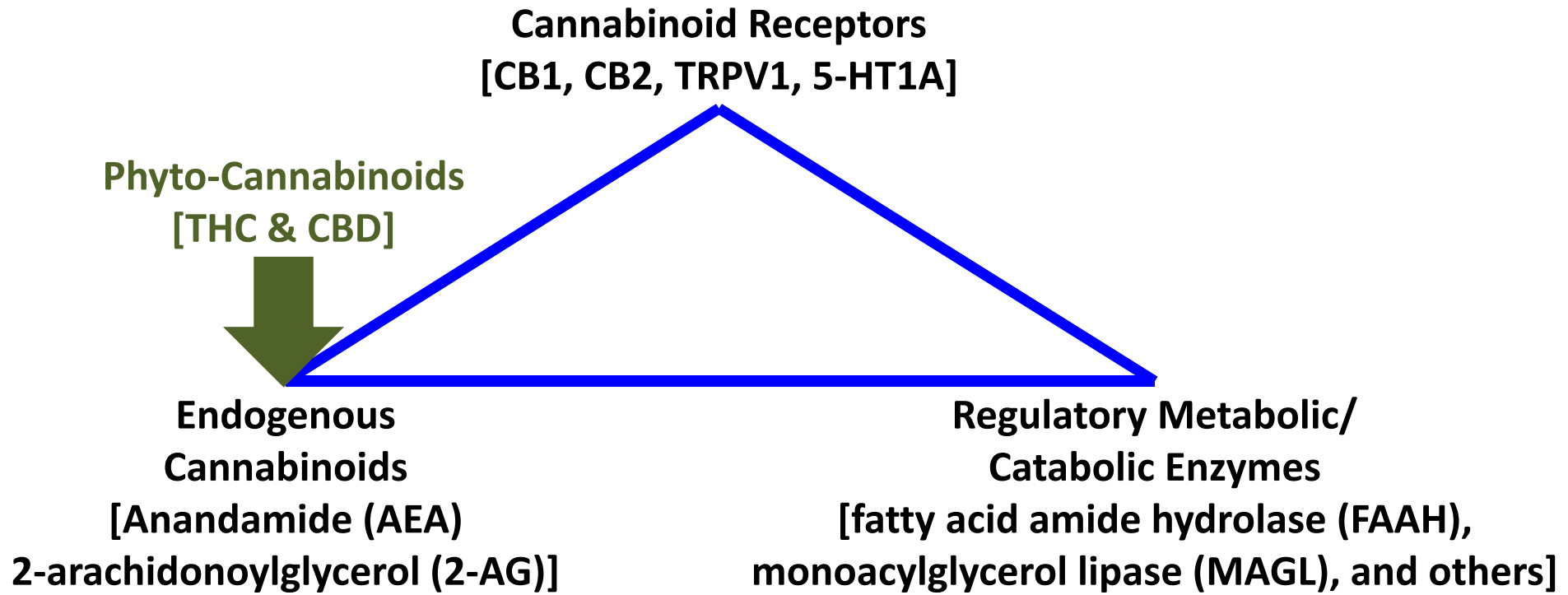
*Hyperactive/  
Too much stimulation*

# Endocannabinoid Tone

- Most important physiologic system involved in establishing and maintaining human health
- Various lifestyle factors including diet and aerobic activity affect the overall ECS function or *'endocannabinoid tone'*
- Keeps internal bodily functions stable and controls how we *think, feel, and react*
- *The Autonomic Nervous System*



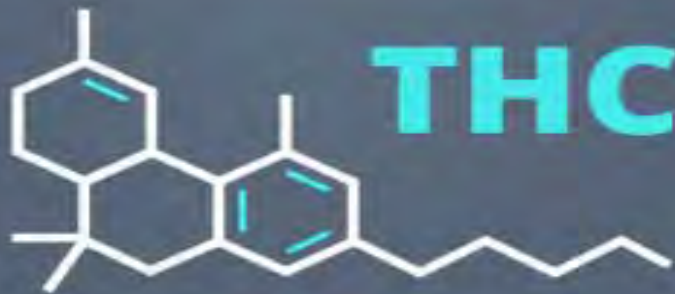
# Nature and the Endocannabinoid System



## Cannabinoids in the Body

80+

cannabinoid  
compounds are found  
in cannabis plants



(Delta-9-tetrahydrocannabinol)



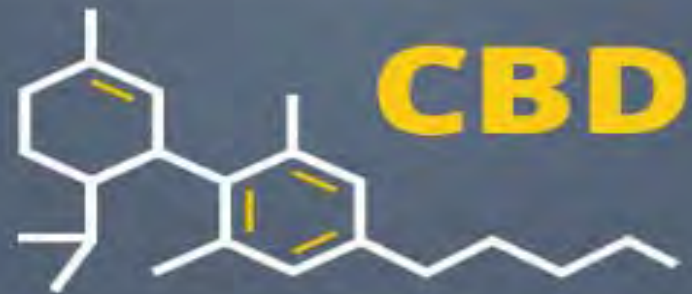
Psychoactive



Creates the characteristic  
marijuana "high"



Can **relieve pain**  
and inflammation



(Cannabidiol)



Non-psychoactive



Can **reduce negative**  
psychoactive effects of THC



Responsible for many of the  
**medical benefits** of cannabis

## EFFECTS

**THC**

**CBD**

**Analgesic**  
Relieves pain and inflammation

**Relaxation**  
Creates sense of relaxation and well-being

**Drowsiness**  
Induces sleep

**Euphoria**  
Creates "high"

**Appetite Stimulant**  
Creates urge to eat

**Anti-depressant**  
Combats anxiety and depression

**Anti-convulsant**  
Suppresses seizure activity

**Anti-oxidant**  
Combats neuro-degenerative diseases

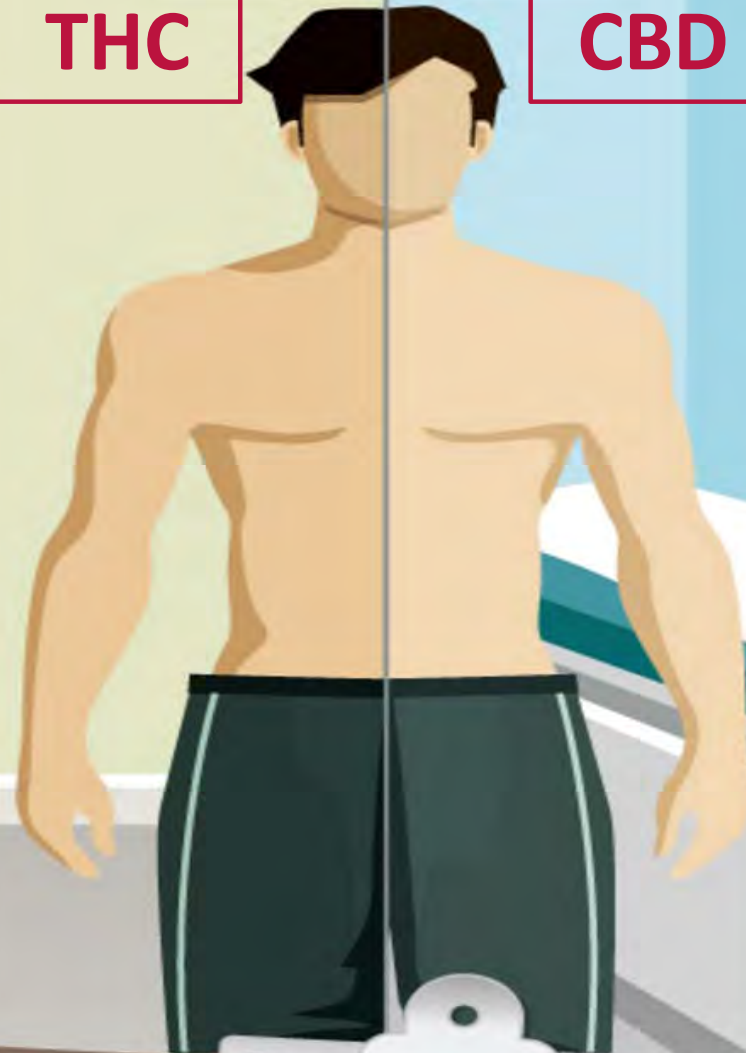
**Anti-psychotic**  
Combats psychosis

**Neuro-protective**  
May protect neurons in the brain

**Anti-emetic**  
Reduces nausea and vomiting

**Anti-inflammatory**  
Combats inflammation and pain

**Anti-tumoral**  
Combats tumor and cancer cells



# What is Difference Between THC & CBD?

## Tetrahydrocannabinol (THC)

- Psychoactive or “high”
- Mimics anandamide
- Anxiogenic
- Paranoia potential
- Stimulates appetite
- Sleep inducing

## Cannabidiol (CBD)

- Non-psychoactive
- Counters THC effects
- Anxiolytic
- Anti-psychotic
- Decreases appetite
- Promotes wakefulness

# Side Effects

## THC



**Anxiety and paranoia are well-known potential side effects**

**May have acute and long-term adverse effects on parts of brain for learning and memory**

## CBD



**Immediate and long-term side effects appear to be minimal**



# Safety of CBD

The alterations in thinking and perception caused by THC are not observed with CBD. The different pharmacological properties of CBD give it a different safety profile from THC.

A review of 25 studies on the safety and efficacy of CBD did not identify significant side effects across a wide range of dosages, including acute and chronic dose regimens, using various modes of administration.

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**Nora D. Volkow, Director, National Institute on Drug Abuse**  
Testimony on June 24, 2015, to Senate Caucus on International Narcotics Control

# CBD: Preclinical and Clinical Evidence

**Anti-Seizure Effects:** Elimination or decreased frequency of seizures

**Neuroprotective and Anti-Inflammatory Effects:** Alzheimer's, stroke, glutamate toxicity, multiple sclerosis, Parkinson's disease, and neurodegeneration caused by alcohol abuse

**Analgesic Effects:** Efficacy on central and peripheral neuropathic pain, rheumatoid arthritis, and cancer pain

**Anti-Tumor Effects:** Antioxidant/anti-inflammatory effects

**Anti-Psychotic Effects:** May mitigate, particularly induced by THC

**Efficacy for Treating Substance Use Disorders:** Reduced rewarding effects of morphine and reduced cue-induced heroin seeking

**Anti-Anxiety, Stress Reduction Effects:** Reducing behavioral and physiological measures of stress and anxiety



***Common Effects:***

- euphoria
- relaxation
- anxiety
- short term memory impairment

# Symptoms Following Brain Injury

 <b>Thinking/ Remembering</b>	 <b>Physical</b>
Difficulty thinking clearly	Headache Fuzzy or blurry vision
Feeling slowed down	Nausea or vomiting (early on) Dizziness
Difficulty concentrating	Sensitivity to noise or light Balance problems
Difficulty remembering new information	Feeling tired, having no energy



 <b>Emotional/ Mood</b>	 <b>Sleep</b>
Irritability	Sleeping more than usual
Sadness	Sleep less than usual
More emotional	Trouble falling asleep
Nervousness or anxiety	

# How CBD Treats Anxiety (Mechanisms)

- **Blocks FAAH enzyme from breaking down anandamide increasing its levels in the brain**
- **Serotonin 5-HT1A receptor (partial agonist)**
  - **CBD (but not THC) binds to receptor, but only stimulates partially**
  - **Displaces agonists in dose-dependent manner**
  - **Results in increased serotonin, dopamine**
- **Hippocampal neurogenesis**
  - **Stimulation of CB1/CB2 receptor sites upregulates endocannabinoid signaling leading to growth**

*INDIRECT  
INTERACTION*



**Cannabinoid**



OUTSIDE  
CELL

INSIDE  
CELL

**AILMENTS CBD  
MAY DECREASE:**

- side effects of THC, e.g. anxiety

# CBD's Therapeutic Impact



**Activates 5-HT1A serotonin receptor.** Helps with **anxiety, addiction, appetite, sleep, nausea, vomiting.**



**Binds to TRPV1 receptors.** Moderates **pain, inflammation, body temperature**



**Blocks G protein receptor GPR55.** May decrease **bone reabsorption** and the spread of **cancer cells.**



**Activates peroxisome proliferator activated receptors (PPARs).** Has been shown to produce **anti-cancer effect** and help with **Alzheimer's.**





# CBD as an Antidepressant

- Study results demonstrate that CBD exerts fast and maintained antidepressant-like effects
- CBD significantly enhanced serotonin and glutamate levels
- CBD could represent a novel fast antidepressant drug, via enhancing both serotonergic and glutamate cortical signaling through a 5-HT1A receptor-dependent mechanism

Cannabidiol induces rapid-acting antidepressant-like effects and enhances cortical 5-HT/glutamate neurotransmission: role of 5-HT1A receptors. Linge et al. *Neuropharmacology*. 2016 Apr;103:16-26.



# Cannabinoids for Psychiatric Sx

- CBD is emerging as potential treatment for:
  - Psychosis
  - Anxiety disorders
  - Addictive behavior

Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Devinsky, et al.  
*Epilepsia* 55(6): 791–802



# Psychosis

- **Current antipsychotics block dopamine D2 receptors (D2R), a mechanism that doesn't treat the underlying cause or neurochemical disorder**
- **Acute schizophrenia RCT compared CBD and a standard antipsychotic in 33 patients over 4 weeks. Both groups showed highly significant improvements. CBD had better improvement of negative symptoms and a significantly superior safety profile, lacking amisulpride's extrapyramidal symptoms, weight gain, and elevated serum prolactin.**
- **In fMRI studies, CBD alters brain function in the limbic and neocortical areas that show abnormalities in schizophrenia. In healthy subjects, the acute psychotomimetic effects of  $\Delta^9$ -THC correlated significantly with attenuation of striatal activation during a verbal memory task, whereas CBD augments striatal activation in the same task.**



# Anxiety disorders

- CBD reduces anxiety in a simulated public-speaking task
- A more recent study in patients with social anxiety disorder confirmed an anxiolytic effect of CBD, and SPECT analysis showed that this was associated with alterations in blood flow in limbic and paralimbic brain areas
- A significant anxiolytic effect has also been demonstrated during emotional processing following exposure to neutral, mildly fearful, and intensely fearful visual cues
- fMRI revealed that this effect correlated with decreased left amygdala activity, an effect opposite of that seen following THC treatment



# Addictive Behavior

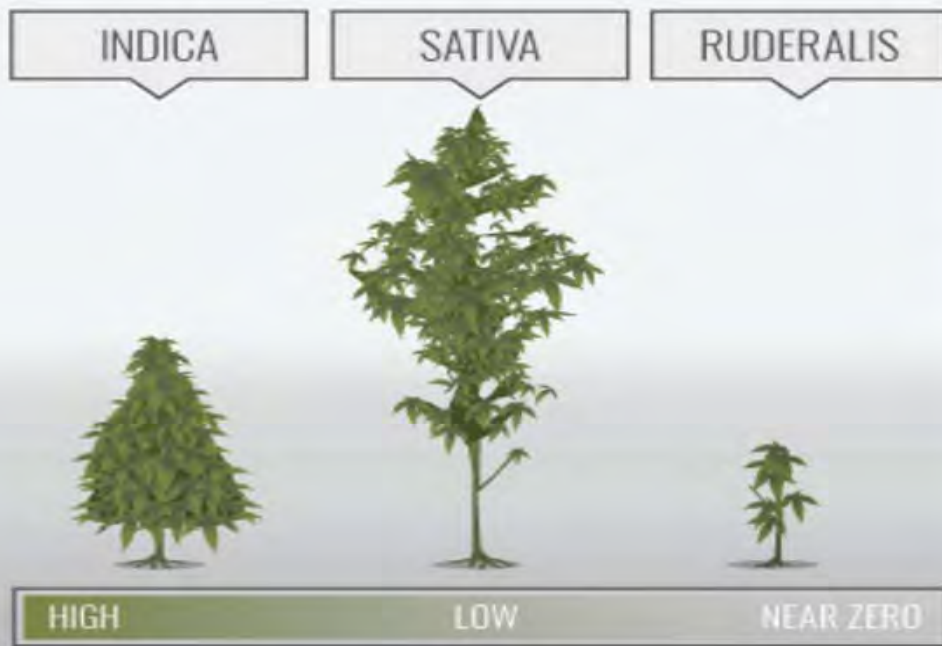
- **Animal models of heroin- and stimulant-dependence show that CBD reduces drug-seeking behavior**
  - **In a study using cocaine and amphetamine in rats, THC and CBD potentiated the extinction of stimulant-dependence behavior without altering learning or memory retrieval**
  - **CBD inhibits heroin-seeking behaviors and normalized drug-induced changes within the nucleus accumbens for up to 2 weeks suggesting long-term impact relevant to drug relapse**
- **Smokers of higher CBD:THC showed lower attentional bias to drug stimuli and lower self-rated liking of cannabis stimuli in 94 cannabis users**
- **CBD therapeutic for cannabis withdrawal and nicotine dependence**



THC is found in cannabis plants.

### Cannabis

A flowering plant with three species:



THC/CBD RATIO

*Ratios highly variable based on individual strains.*

CBD is found in both cannabis plants and industrial hemp plants.

### Industrial hemp

One of the earliest domesticated plants by humans.

Hemp is actually cannabis sativa that has been selectively bred to be **taller, fibrous, and strong.**

Hemp has only tiny traces of THC.



# ***Cannabis sativa***



## **Marijuana**

- **THC content 5-30%**
- **Cultivated for THC from budding flowers**
- **Grown under controlled conditions**
- **Classified as illegal drug**
- **Use: Recreational/  
medical drug**

## **Hemp**

- **THC content <0.3%**
- **Cultivated like bamboo: tall, thick, fast growing**
- **Grown outside >20 ft**
- **Classified as food, legal to import into U.S.**
- **Use: Foods, oils, textiles, rope, fabrics**



# Comparing Hemp to Medical Cannabis

## Agricultural Hemp

- Grown outdoors
- Sequesters CO2
- Environmentally Helpful
- Requires 80% less water
- Energy provided by the sun
- No pesticides required
- Textbook Sustainability

## Medical Cannabis

- Enormous Carbon Foot Print
- Environmentally Harmful
- Wasteful Water Demands
- Huge Strain on Power Grid
- Consequences of Fungicides, Pesticides and Fertilizers
- Unsustainable



# CB1 & CB2 Receptors

## The Body's Natural Endocannabinoid System

- CB1 & CB2 – These 2 receptors in the body that bind with cannabinoids to promote homeostasis for the overall health and wellness.
- According to a study published by the Public Health Institute, 92% of medical cannabis patients agree that this is due to the role cannabinoids play in the brain, as well as throughout all the major neural networks.
- CB1
  - Brain, Lungs, Vascular System, Muscles, Reproductive Organs
- CB2
  - Colon, Spleen, Bones, Immune System
- CB1 & CB2
  - Pancreas, Liver

# Common Recommendations

- NEUROLOGIC IRRITABILITY
  - Anxiety\*\*\*
  - Neuropathy
  - Insomnia\*\*\*
  - Neuropathic Pain\*\*\*
- INFLAMMATION
  - Osteoarthritis
  - Rheumatologic Disease
  - Ulcerative Colitis
  - Crohns

# Common Recommendations

- AUTONOMIC DYSFUNCTION
- FOOD SENSITIVITIES
- CHEMOTHERAPY SIDE EFFECTS

# DISEASE MANAGEMENT OPPORTUNITIES

- NEUROLOGIC
  - Parkinson's
  - Alzheimer's/Dementia
  - Huntington's chorea
  - Multiple Sclerosis

# How Much Do I Take?

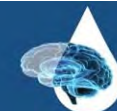
- Here are some unverified examples reported:
  - To treat chronic pain:
    - 2.5 - 40 mg of CBD 1-2 times daily, for up to 25 days
  - To treat sleep disorders:
    - 15 – 200 mg of CBD by mouth prior to sleep
  - To treat wellness & recovery:
    - 2.5 – 10 mg of CBD 1-2 times daily
- More often intervals for anxiety instead of more CBD
- Glaucoma – over 40 mg might increase eye pressure
- Cancer
- MS
- Autism
- Epilepsy

# Potential Side Effects

- Reported adverse effects of CBD are mostly mild including:
  - Drowsiness
  - Diarrhea
  - Fatigue
  - Decreased appetite.

# Practical Notes on Using CBD

- **Rule #1: low doses – start low and gradually ↑**
- **High doses may overwhelm CB1 receptors and ↑spaciness and anxiety**
- **Very safe: no receptors in Respiratory & C-V nuclei**
- **Positive interaction with the Limbic system: stress, anxiety , fear, emotions**
- **Good quality CBD in measured doses is important**
- **Possibly synergistic with The Omega-3 Protocol**





# Important Reminders

- CBD drug interaction and side effect documentation is limited. Check with your healthcare practitioner for additional guidance.
- These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Questions?

