

กัญชาทางการแพทย์ Cannabis in Modern Medicine

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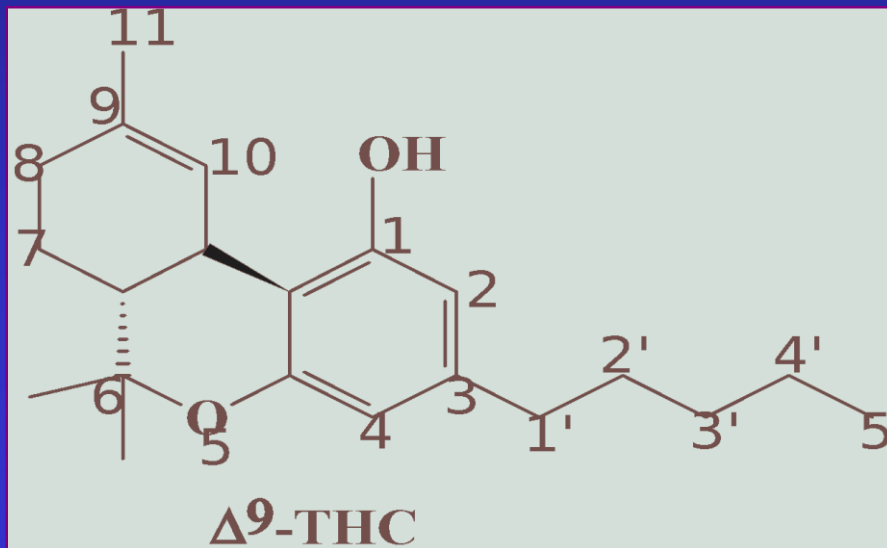
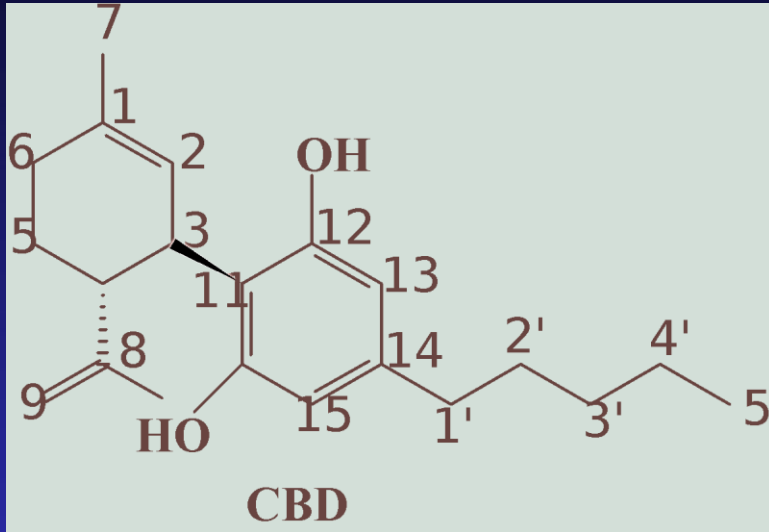
Endocannabinoids
Phyto cannabinoids
Synthetic cannabinoids

Endocannabinoids

Evidence supports the role of endocannabinoids in:

- Immune function
- Inflammation
- Appetite
- Metabolism and energy homeostasis
- Cardiovascular function
- Digestion
- Bone development and bone density
- Pain
- Reproduction
- Psychiatric disease
- Psychomotor behavior
- Memory
- **Wake/sleep cycles**
- Regulation of stress and emotional state
- Learning

Cannabinoids



- Cannabis contain ~500 chemicals
- Compounds with a skeleton made of a resorcinol type ring with a terpene moiety derivative attached to it (around 70 identified)
- 80+ cannabinoids (21-carbon molecule)
- Among cannabinoids, THC and Cannabidiol (CBD) are the most abundant.

Some of the more prominent cannabinoids include:

- Delta-9-tetrahydrocannabinol (THC)
- Cannabidiol (CBD)
- Cannabinol (CBN)
- Tetrahydrocannabivarin (THCV)
- Cannabichromene (CBC)
- Cannabicyclol (CBL)
- Cannabidivarin (CBDV)
- Yet still another est. 80-100 other cannabinoids

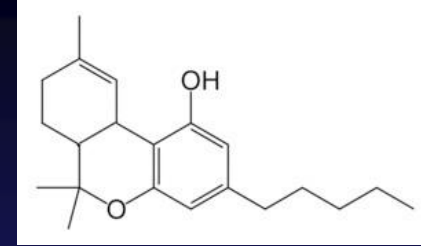
CLINICAL PHARMACOLOGY OF CANNABIS

- 95-99% plasma protein bound
- Hydroxylation, oxidation, and conjugation for rapidly clearance from plasma
- 1st-pass metabolism with oral admin(11-OH-THC)
- Elimination over several days (adipose)
- Breast milk distribution, Pregnancy Category C
(พบว่ายามีความเสี่ยงต่อการเกิดความผิดปกติของตัวอ่อนในครรภ์ แต่ไม่มีการศึกษาการใช้ยาในหญิงมีครรภ์)
- Excretion: days to wks 20-35% found in urine
- 65-80% found in feces

CLINICAL PHARMACOLOGY OF CANNABIS

- 5% as unchanged drug (when given PO)
- Synthetic THC, called dronabinol, does not contain CBD, CBN, or other cannabinoids, which is one reason why its pharmacological effects may differ significantly from those of natural *Cannabis* preparations (Entourage effect).

THC (Delta-9-Tetrahydrocannabinol)



- 1964 - THC, Main Psychoactive Component of Cannabis, First Identified and Synthesized by **Dr. Raphael Mechoulam**, Professor of Medicinal Chemistry at the Hebrew University of Jerusalem
- He is the first to identify **delta-9-tetrahydrocannabinol (THC)**, as the main **psychoactive component** of cannabis.
- **Delta-9-THC and Delta-8-THC** are the only compounds in the marijuana plant that produce all the psychoactive effects of marijuana.

The Human Endocannabinoid System

CBD, CBN and THC fit like a lock and key into existing human receptors. These receptors are part of the endocannabinoid system which impact physiological processes affecting **pain modulation, memory, and appetite plus anti-inflammatory effects and other immune system responses.**

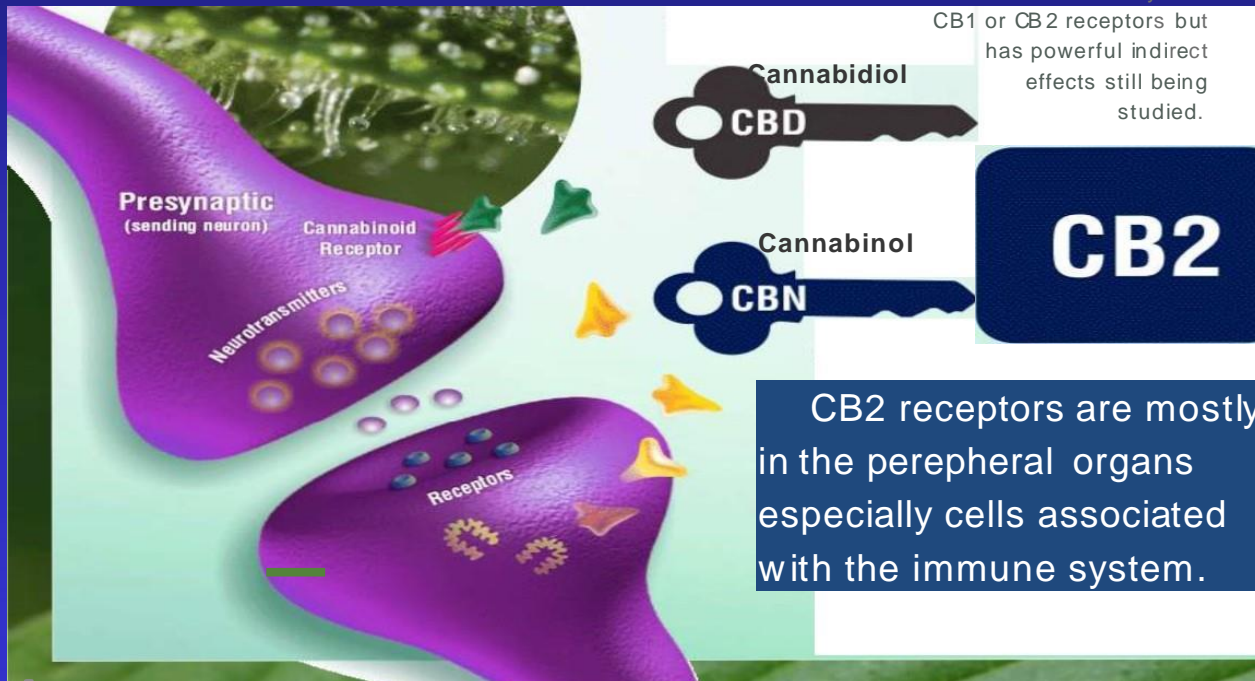
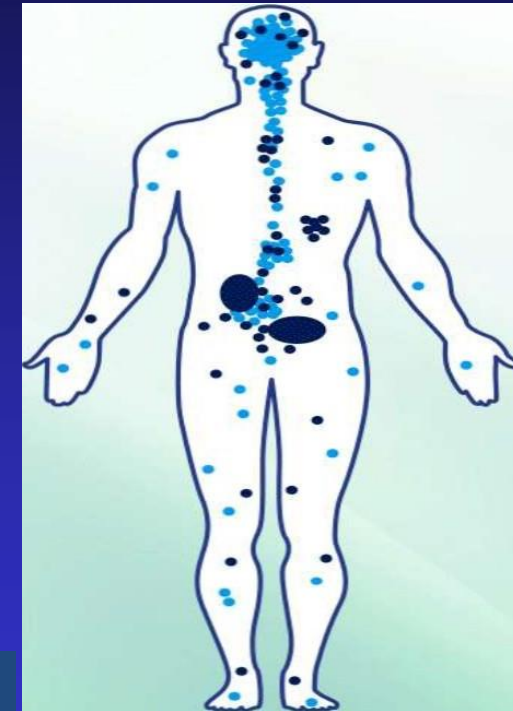
The endocannabinoid system comprises two types of receptors, CB1 and CB2, which serve distinct functions in human health and well-being.



CB1 receptors are primarily found in the brain and central nervous system, and to a lesser extent in other tissues.



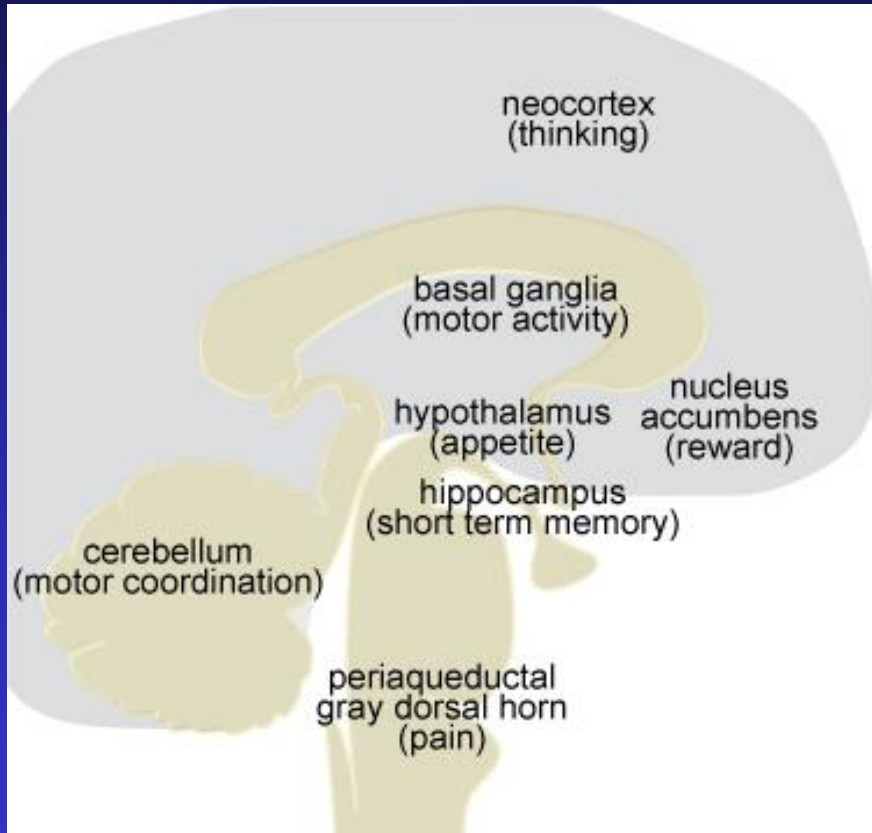
Receptors are found on cell surfaces



CB2 receptors are mostly in the peripheral organs especially cells associated with the immune system.

Distribution of CB1 & CB2 receptors

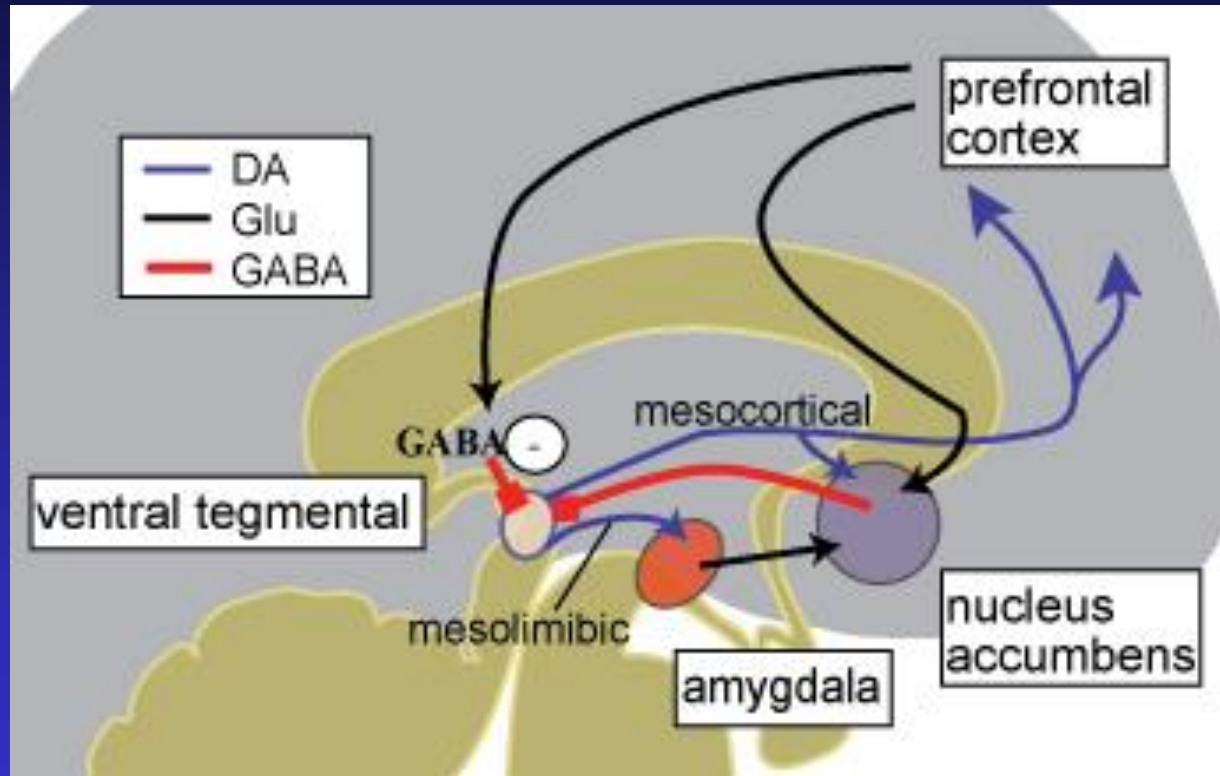
CB1



CB2

immunologic cells (modulation
cell migration)
microglia (possible role in
Alzheimer's?)

Cannabis effect on reward pathway



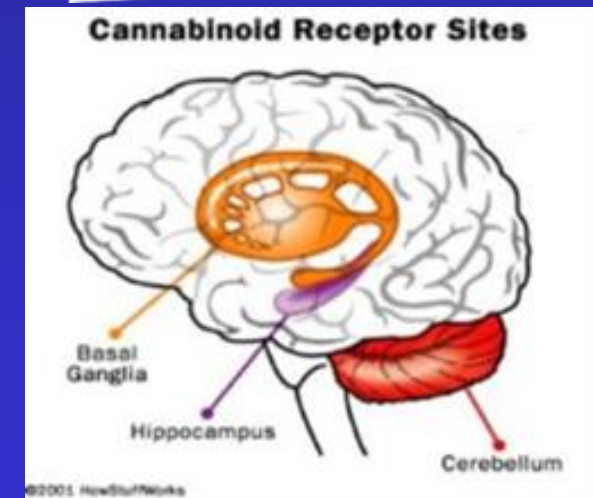
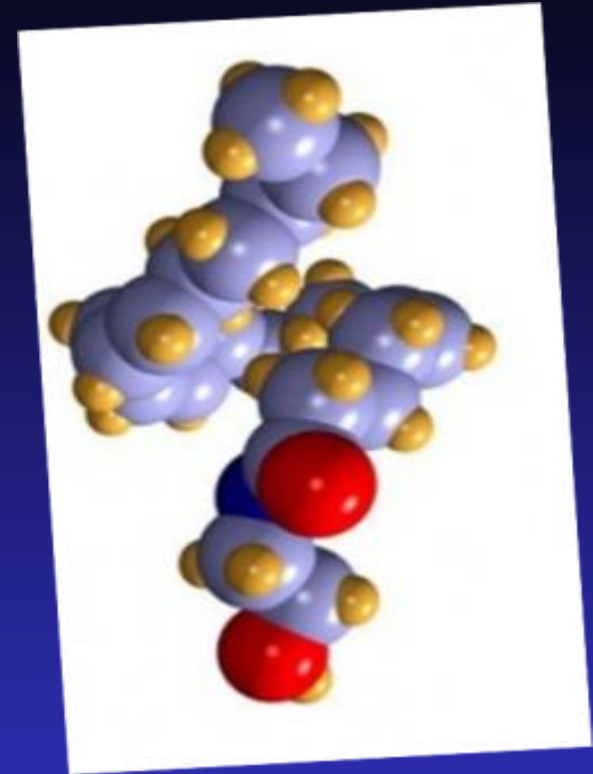
DA: dopamine
reward and
motivation

Glu: Glutamine for
learning and memory

GABA: inhibition of
neuronal activity

Endocannabinoid

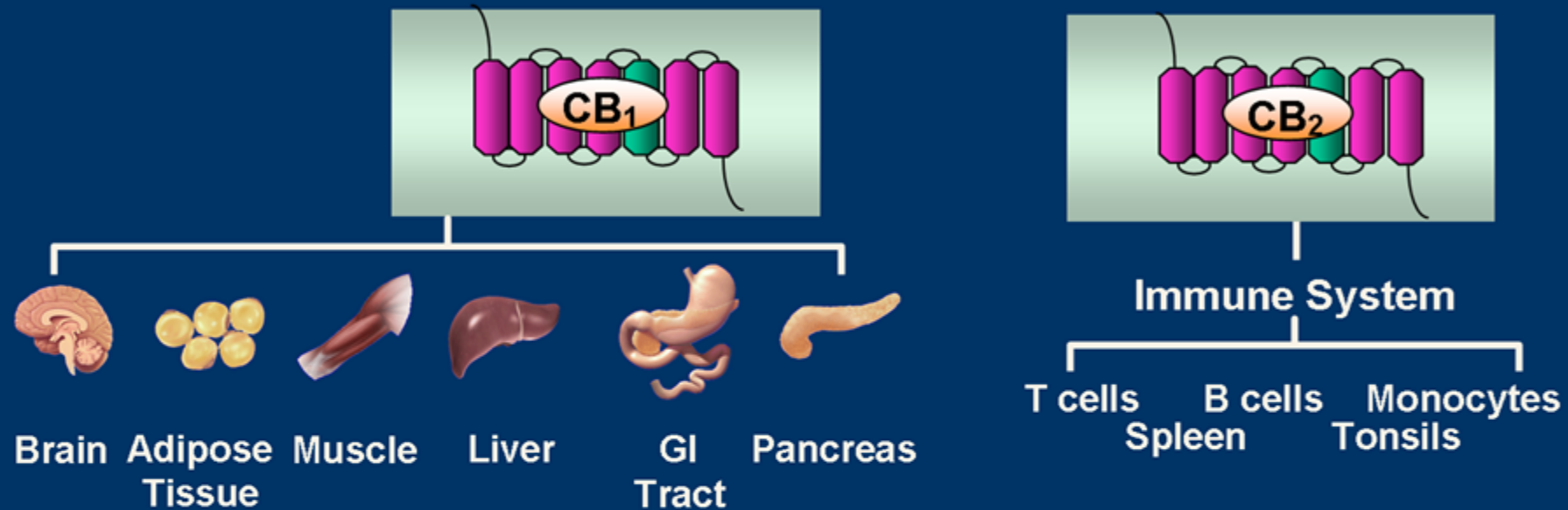
- "28yrs after discovering THC, in 1992, Dr. Mechoulam, Dr. William Devane and Dr. Lumir Hanus, identified the brain's first endogenous cannabinoid (or endocannabinoid) – (the brain's natural THC) -which they called 'Anandamide,' from the Sanskrit word 'ananda,' (means 'eternal bliss' or 'supreme joy').
- ECS is a group of neuromodulatory lipids and their receptors in the brain that are involved in a variety of physiological processes including appetite, pain-sensation, mood, and memory;
- It mediates the psychoactive effects of cannabis
- Vigorous exercise stimulates the release of anandamide, and the sense of euphoric well-being that comes with a healthy workout



Physiological Effects of Endocannabinoids

- Endocannabinoids are often produced as an adaptive response to cellular stress, aimed at reestablishing cell homeostasis
- Endocannabinoids affect a large number of physiologic processes including
 - Feeding behavior
 - Energy balance, metabolism, and GI function
 - Pain perception
 - Motor control and posture
 - Learning, memory, and emotions
 - Immune and inflammatory responses
 - Cardiovascular function
 - Reproduction
 - Bone formation

Cannabinoid Receptors



- G-protein–coupled receptors
- CB₁ receptors highly expressed in the brain
 - CB₁ receptors also found in adipose tissue, liver, muscle, the gastrointestinal tract, pancreas, as well as reproductive and cardiovascular tissues
- CB₂ receptors are expressed primarily in immune cells
 - CB₂ receptor expression in neurons is being studied

Devane WA et al. *Mol Pharmacol*. 1988;34:605-613.

Munro S et al. *Nature*. 1993;365:61-65.

Ameri A. *Prog Neurobiol*. 1999;58:315-348.

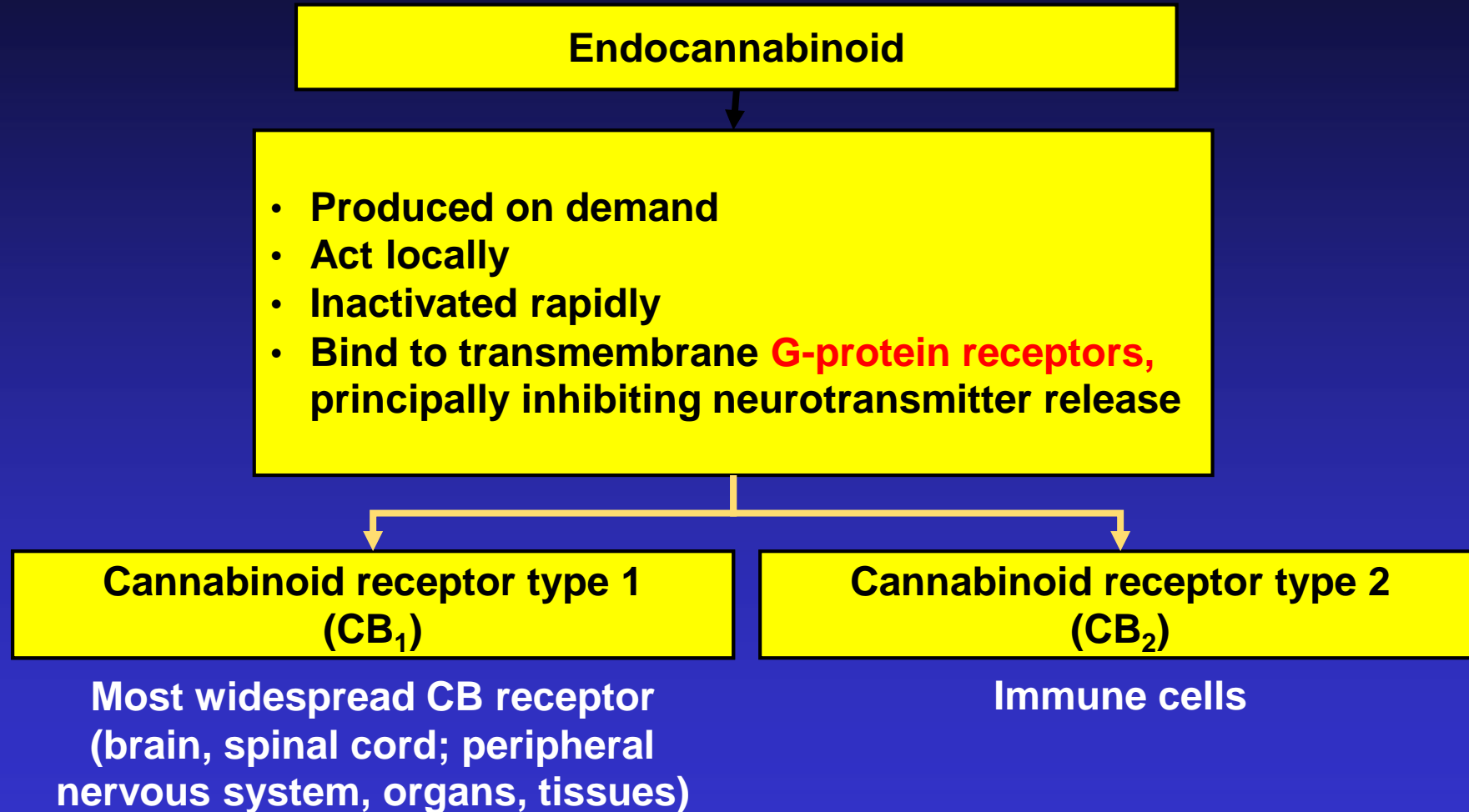
Osei-Hyiaman D, DePetrillo M, Pacher P, et al. *J Clin Invest*. 2005;115:1298-1305.

Cota D, Woods SC. *Curr Opin Endocrinol Diabetes*. 2005;12:338-351.

Location of Cannabinoid Receptors

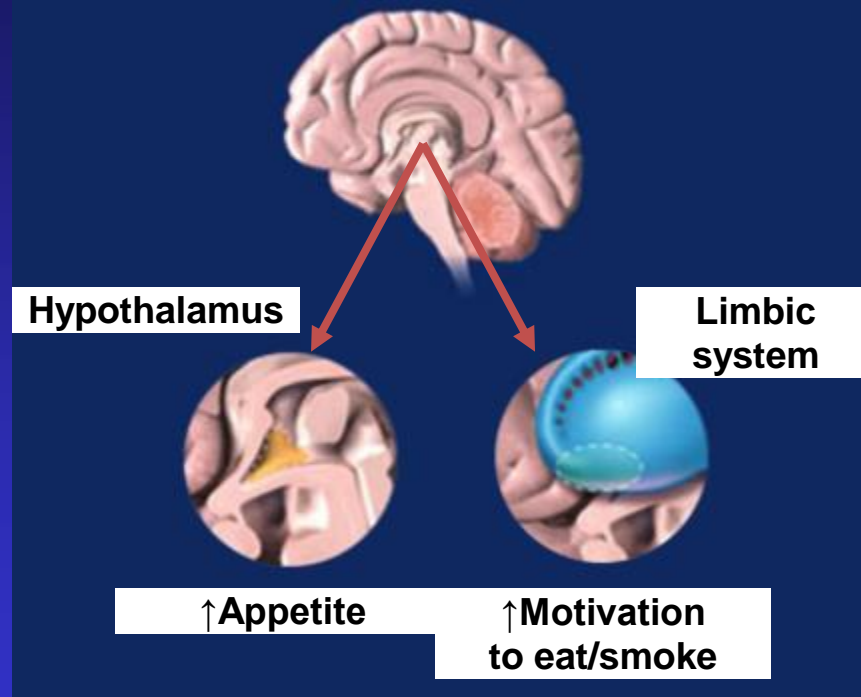
Location	Structure	Function
CB₁ receptors		
CNS	Hippocampus	Memory storage
	Cerebellum	Coordination of motor function, posture, balance
	Basal ganglia	Movement control
	Hypothalamus	Thermal regulation, neuroendocrine release, appetite
	Spinal cord	Nociception
	Cerebral cortex	Emesis
	Periphery	Lymphoid organs
Vascular smooth muscle cells		Control of blood pressure
Duodenum, ileum, myenteric plexus		Control of emesis
Lung smooth muscle cells		Bronchodilation
Eye ciliary body		Intraocular pressure
CB₂ receptors		
Periphery	Lymphoid tissue	Cell-mediated and innate immunity
	Peripheral nerve terminals	Peripheral nervous system
	Retina	Intraocular pressure
CNS	Cerebellar granule cells mRNA	Coordination of motor function

Endocannabinoid system (ECS): Overview

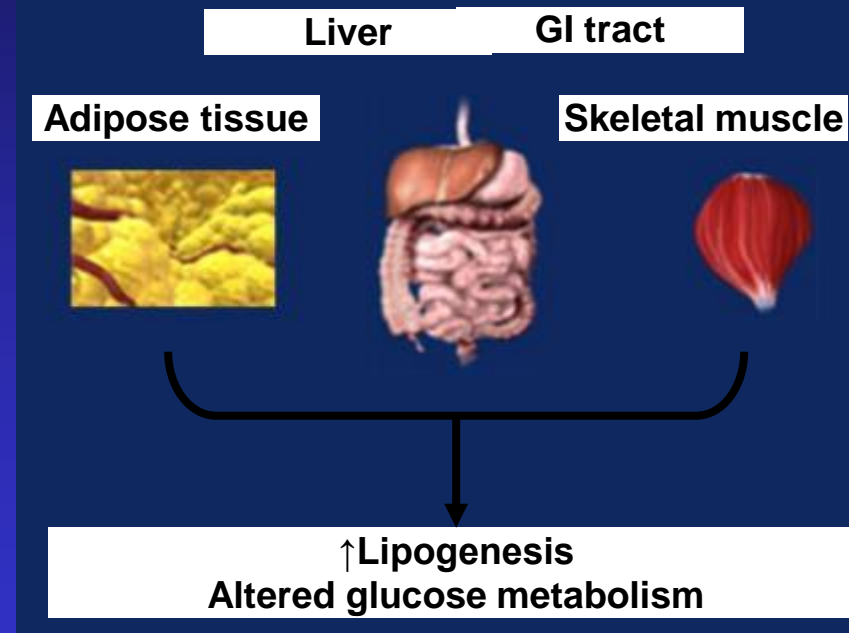


Implications of CB₁ receptor activation

Central nervous system



Peripheral tissue

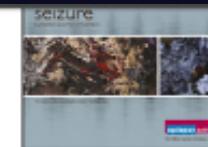


CB₁ knock-out mice

- CB1 cannabinoid receptor knockout in mice leads to **leanness, resistance to diet-induced obesity and enhanced leptin sensitivity**. CB₁ knock-out mice are healthy and live into adulthood [*Int. J. Obes. Relat. Metab. Disord.* 28 (4): 640–8].
- Compared to wildtype, CB₁ knock-out mice exhibit **severe deficits in motor learning, memory retrieval, and increased difficulty in completing the [Morris water maze](#)**.^{[5][53][54]}
- There is also evidence indicating that these knockout animals have an increased incidence and severity of [stroke](#) and [seizure](#).

Endocannabinoids & neuroprotection

- **Anandamide** (arachidonoyl-ethanolamide) and 2-arachidonoyl glycerol (**2-AG**).
- Both anandamide and 2-AG bind to the cannabinoid receptors **CB₁** (present principally in the central nervous system and to a lesser extent in the peripheral nervous system) and **CB₂** (present almost exclusively in the peripheral nervous system).
- These receptors are activated **by THC**, accounting for the effects of cannabis on the nervous system.
- A nonpsychotropic constituent of cannabis, cannabidiol, effectively treats major seizures in animals, and HU-211 (**Dexanabinol®**) is **neuroprotective during brain trauma**.
- Paradoxically, neither **cannabidiol** nor HU-211 binds to **CB₁** or **CB₂** receptors.



Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures

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ABSTRACT

Cannabis sativa has been associated with contradictory effects upon seizure states despite its medicinal use by numerous people with epilepsy. We have recently shown that the phytocannabinoid cannabidiol (CBD) reduces seizure severity and lethality in the well-established *in vivo* model of pentylenetetrazole-induced generalised seizures, suggesting that earlier, small-scale clinical trials examining CBD effects in people with epilepsy warrant renewed attention. Here, we report the effects of pure CBD (1, 10 and 100 mg/kg) in two other established rodent seizure models, the acute pilocarpine model of temporal lobe seizure and the penicillin model of partial seizure. Seizure activity was video recorded and scored offline using model-specific seizure severity scales. In the pilocarpine model CBD (all doses) significantly reduced the percentage of animals experiencing the most severe seizures. In the penicillin model, CBD (≥ 10 mg/kg) significantly decreased the percentage mortality as a result of seizures; CBD (all doses) also decreased the percentage of animals experiencing the most severe tonic-clonic seizures. These results extend the anti-convulsant profile of CBD; when combined with a reported absence of psychoactive effects, this evidence strongly supports CBD as a therapeutic candidate for a diverse range of human epilepsies.

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FOCUS | 08 APRIL 2019

Cannabis, cannabinoid receptors and endocannabinoid system

Cannabis sativa, also popularly known as marijuana, has been cultivated and used for recreational and medicinal purposes for many centuries. The main psychoactive content in cannabis is Δ^9 -tetrahydrocannabinol (THC). In addition to plant *Cannabis sativa*, there are two classes of cannabinoids – the synthetic cannabinoids (e.g., WIN55212-2) and the endogenous cannabinoids (eCB), anandamide (ANA) and 2-arachidonoylglycerol (2-AG). The biological effects of cannabinoids are mainly mediated by two members of the G-protein coupled receptor family, cannabinoid receptors 1 (CB₁R) and 2 (CB₂R). The endocannabinoids, cannabinoid receptors and the enzymes/proteins responsible for their biosynthesis, degradation and re-updating

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Review Article | Published: 25 June 2018

GPR3, GPR6, and GPR12 as novel molecular targets: their biological functions and interaction with cannabidiol

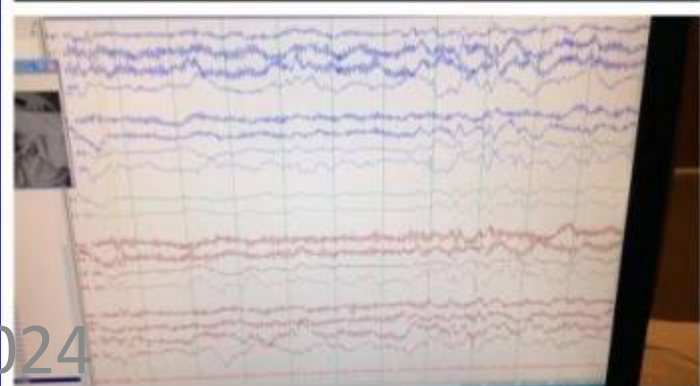
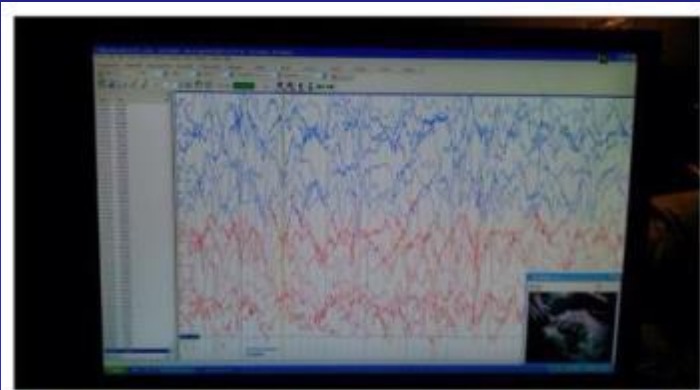
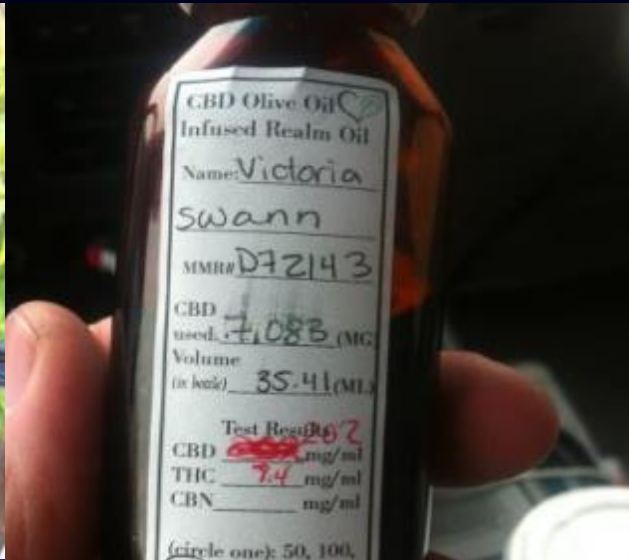
Alyssa S. Laun, Sarah H. Shrader, Zhao-Hui Song

Acta Pharmacologica Sinica **40**, 300–308 (2019) | [Download Citation](#)

Abstract

The G protein-coupled receptors 3, 6, and 12 (GPR3, GPR6, and GPR12) comprise a family of closely related orphan receptors with no confirmed endogenous ligands. These

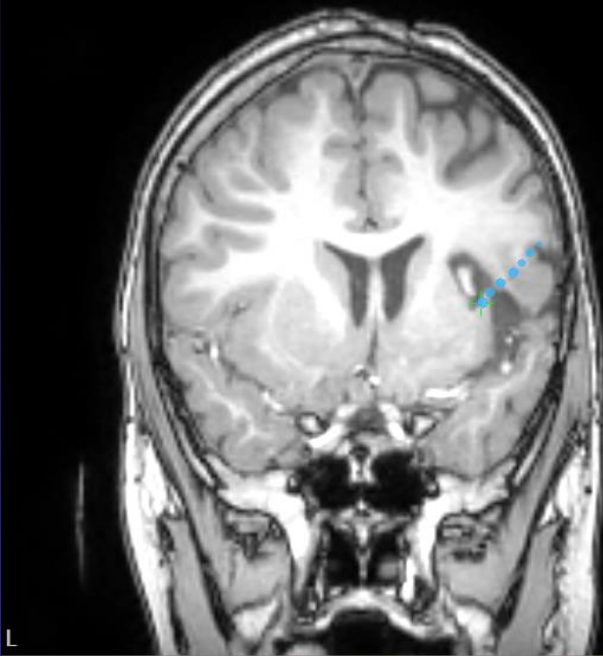
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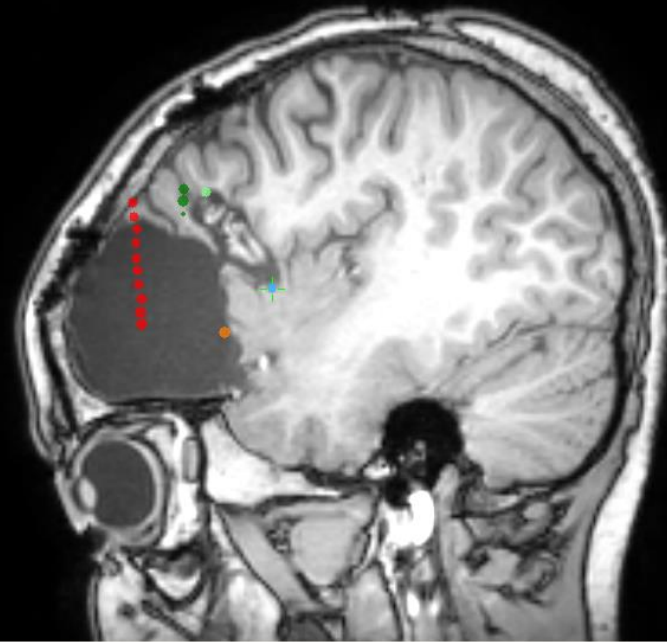
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the link to Charlottes web video is www.theroc.us.

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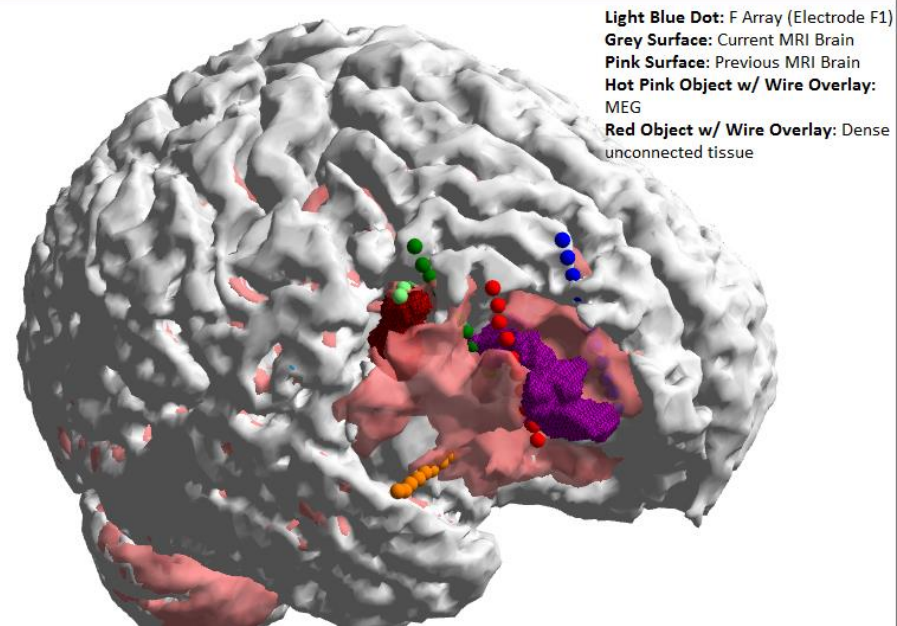
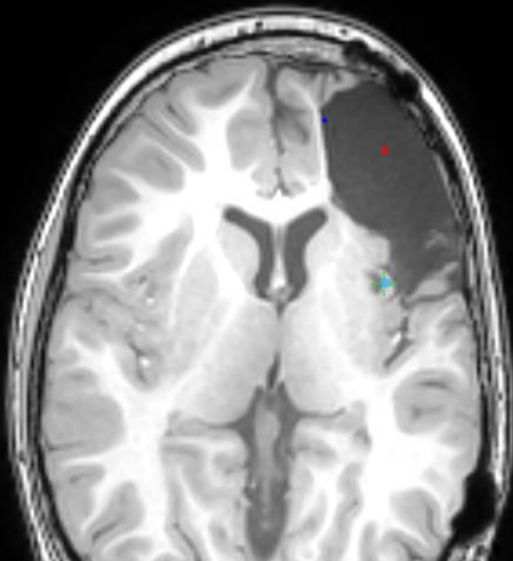


5 0 ms



0 ms

A



Light Blue Dot: F Array (Electrode F1)
 Grey Surface: Current MRI Brain
 Pink Surface: Previous MRI Brain
 Hot Pink Object w/ Wire Overlay:
 MEG
 Red Object w/ Wire Overlay: Dense
 unconnected tissue

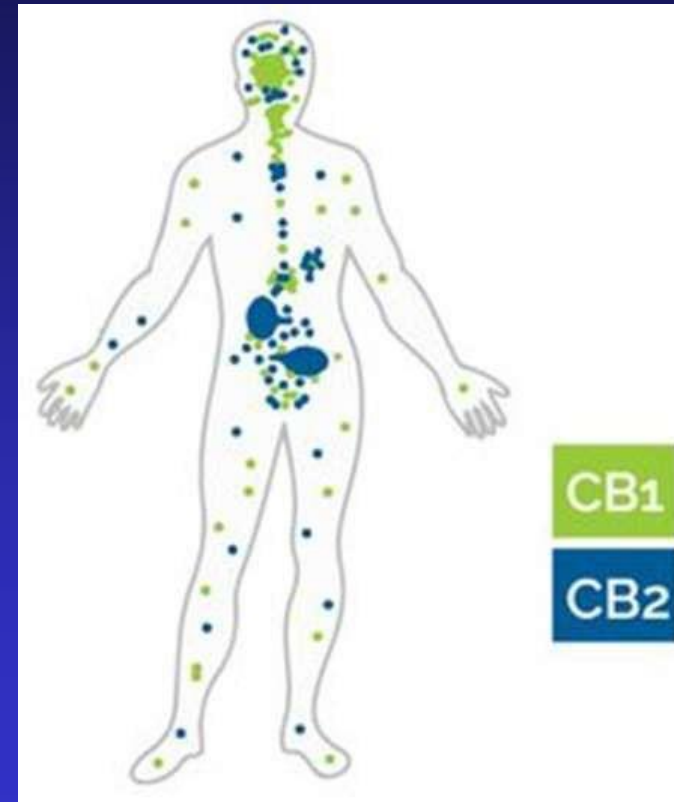
How Does Cannabis Help?

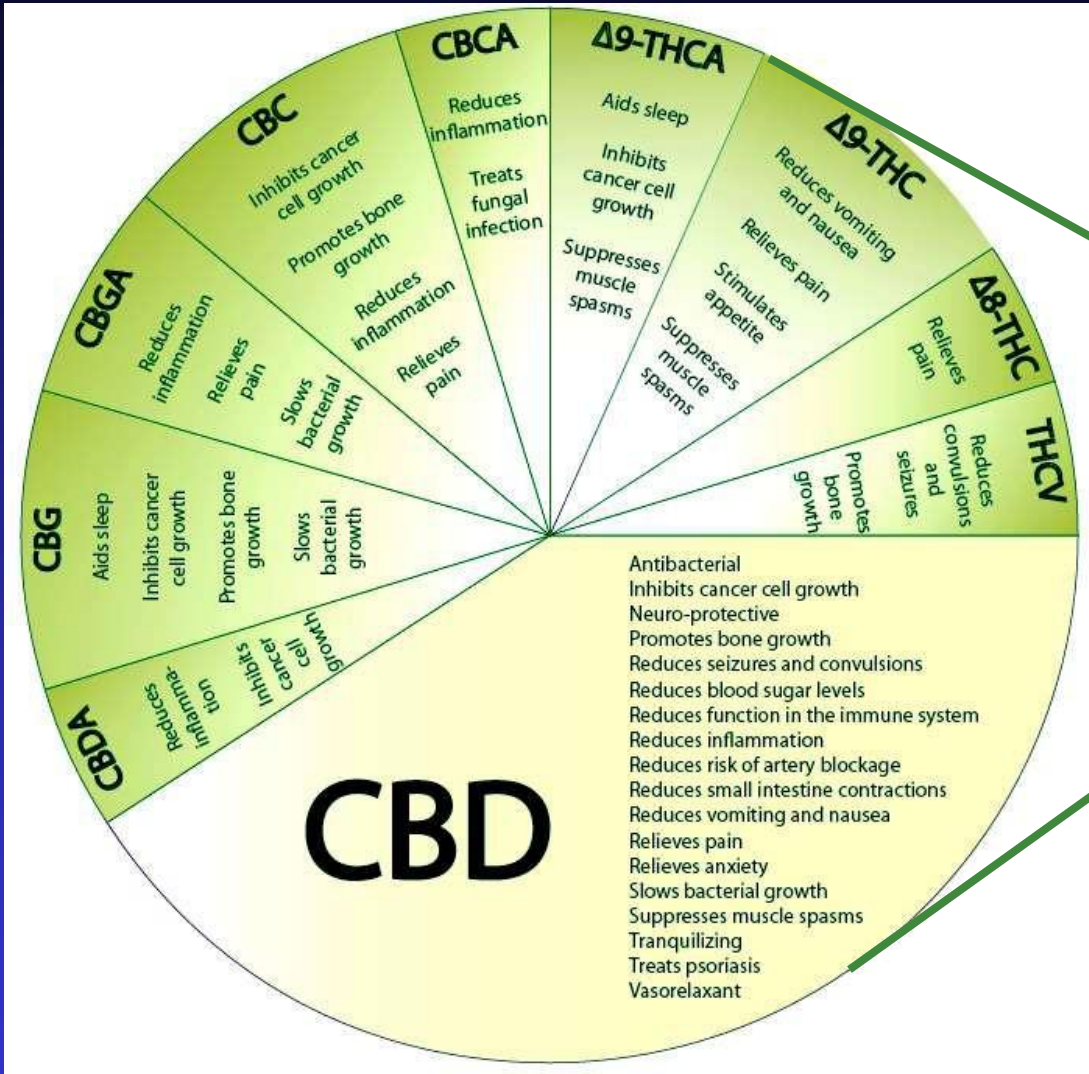
The endocannabinoid system

Receptors found on cells throughout the body

Purpose appears to relate to homeostasis, wherever in the body the receptors are activated by either endo- or phyto-cannabinoids

Image source: David Guzman, "The Endocannabinoid System"



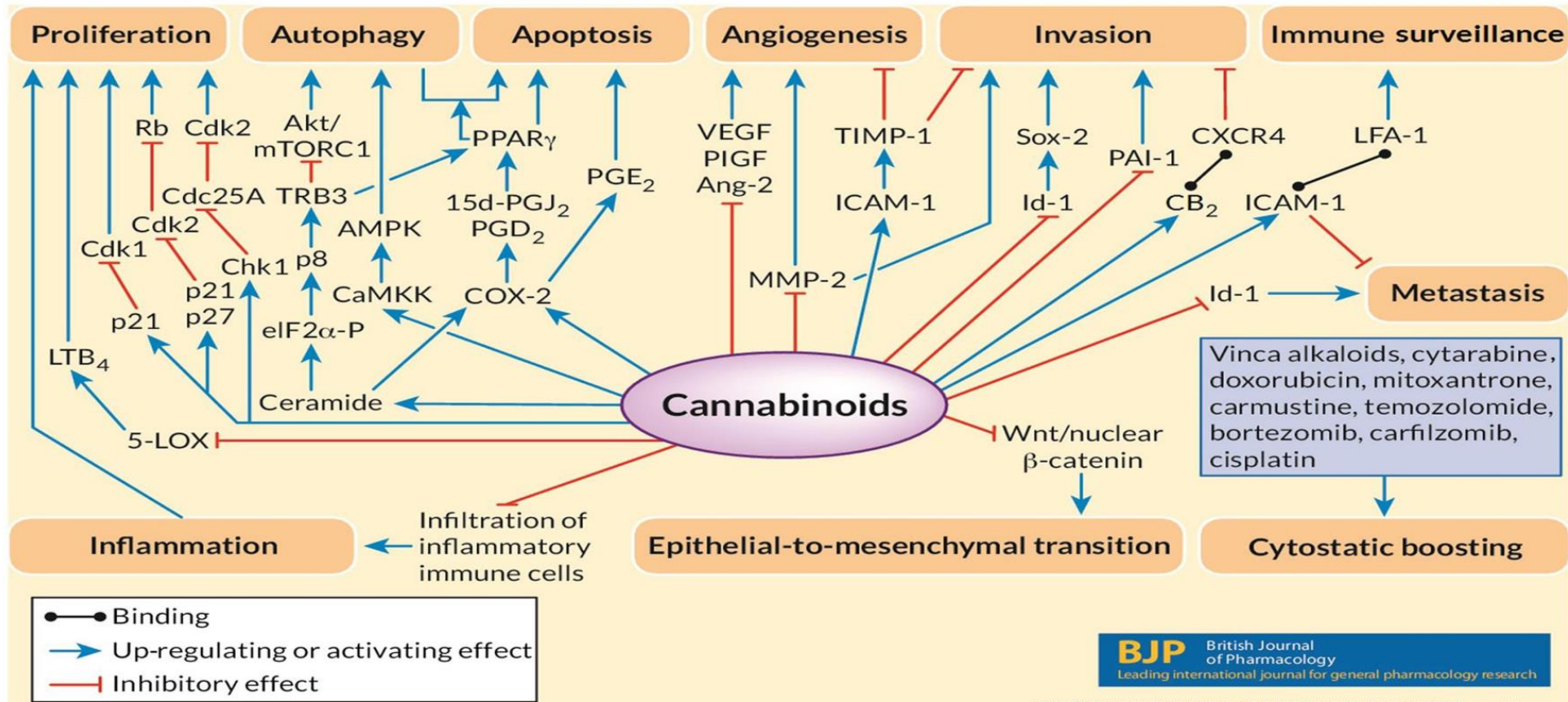


Cannabis Indica

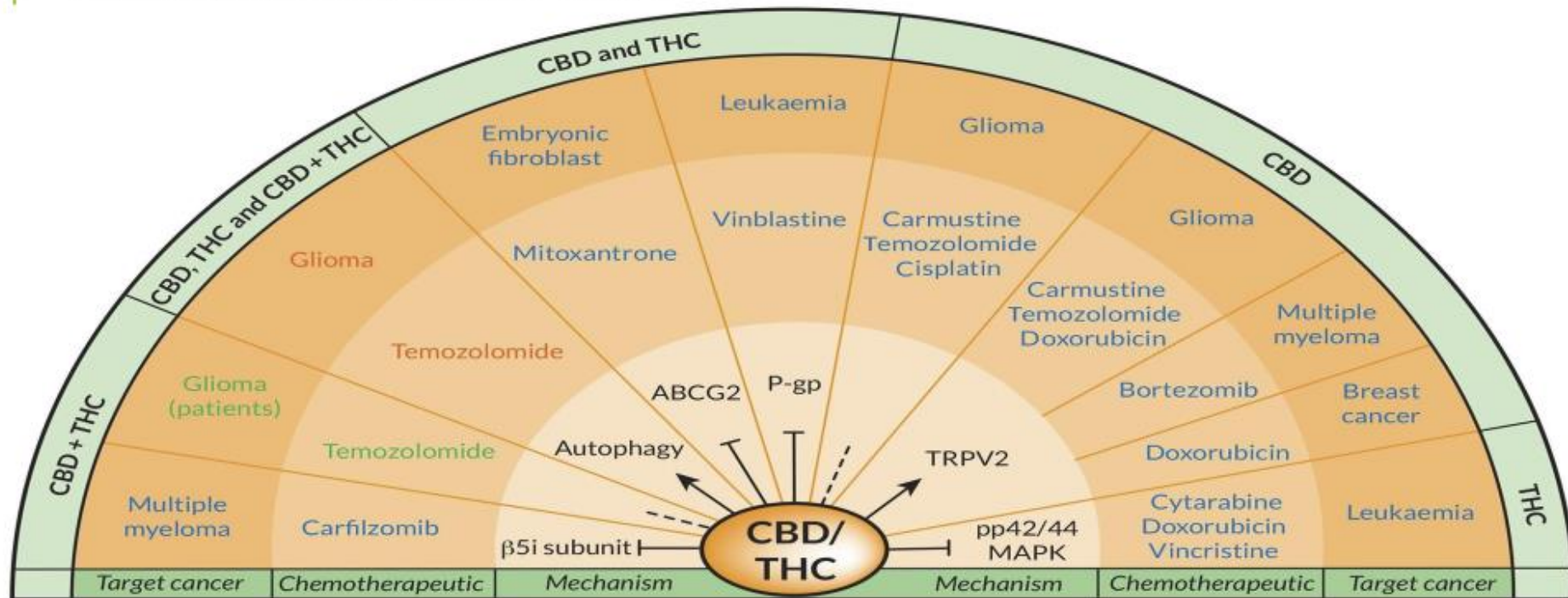


Cannabis Sativa

3. THE FUNCTION OF THE ENDOCANNABINOIDS SYSTEM AND CANNABINOID RECEPTORS



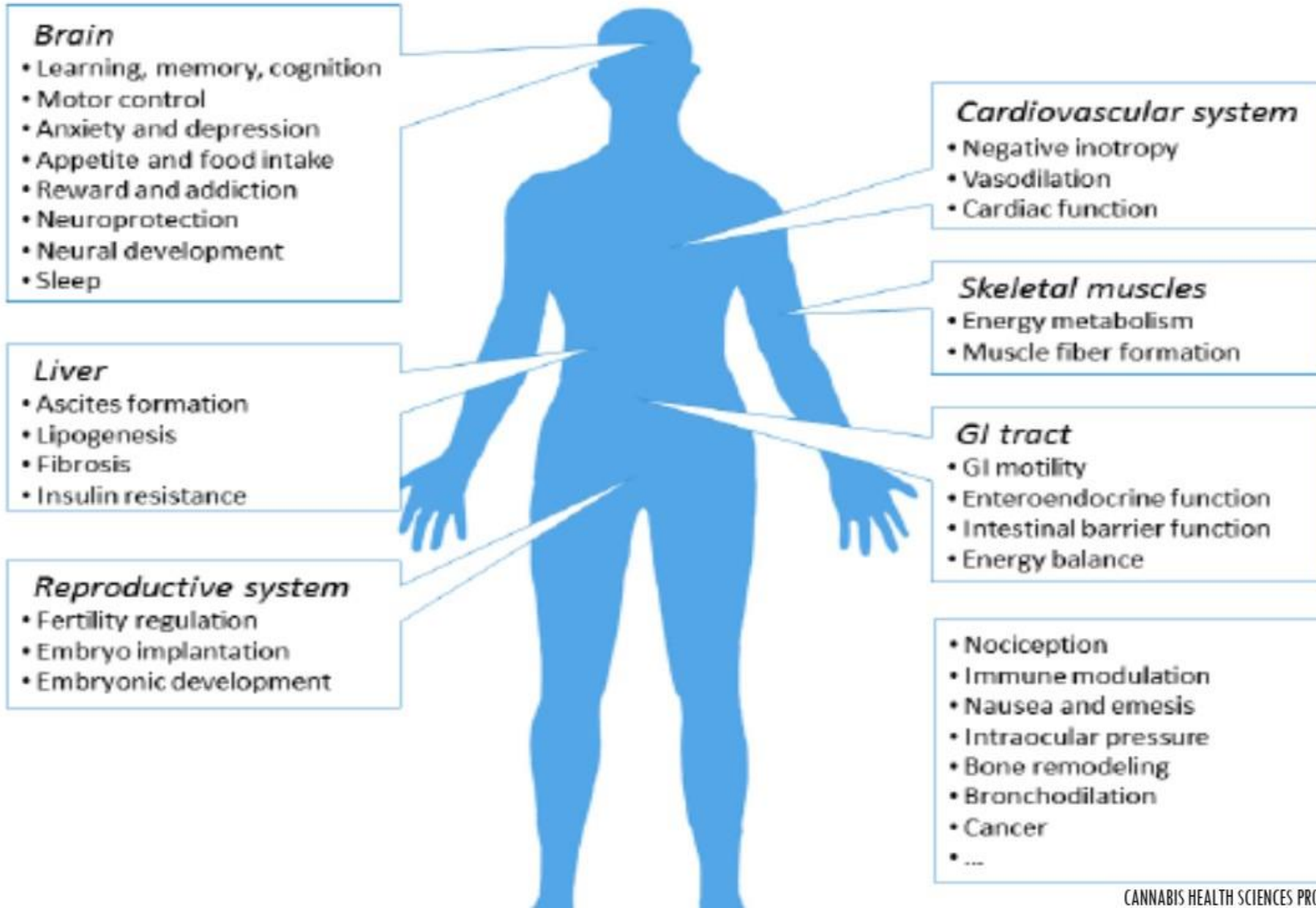
3. THE FUNCTION OF THE ENDOCANNABINOID SYSTEM AND CANNABINOID RECEPTORS



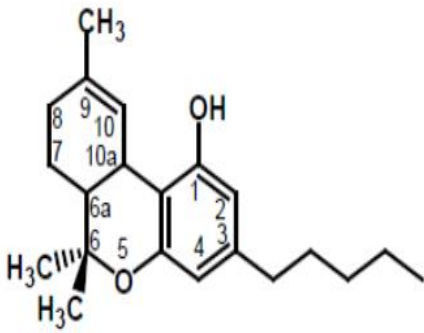
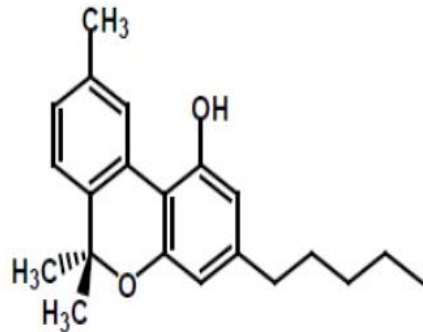
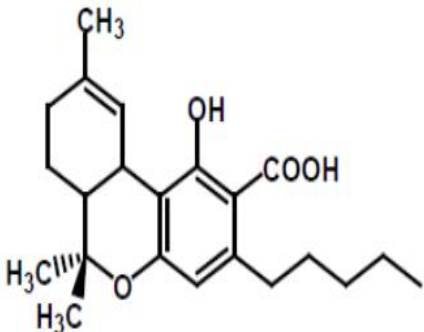
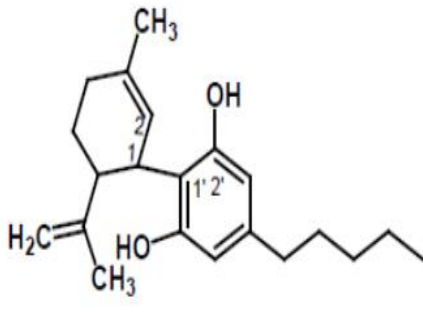
- Mechanism not determined
- Up-regulation, activation
- | Down-regulation, inactivation

BJP British Journal of Pharmacology
 Leading international journal for general pharmacology research

4. PHARMACOLOGY OF EXOCANNABINOIDS



THC VS CBD

<p>(-)-Δ^9-trans-Tetrahydrocannabinol Tetrahydrocannabinol, THC</p>  <p>Main pharmacological characteristics:</p> <ul style="list-style-type: none"> - Euphoriant - Anti-inflammatory - Analgesic - Anti-emetic 	<p>CAS: 1972-08-3 Empirical formula: $C_{21}H_{30}O_2$ Molecular weight: 314.46 g/mol Melting point: viscous oil pKa: 10.6 log P: 6.99 (octanol/water)</p> <p>Solubilities:</p> <p>Water: insoluble (2.8 mg/L 23°C) Ethanol: soluble Chloroform: soluble Hexane: soluble</p>	<p>Cannabinol CBN</p>  <p>Main pharmacological characteristics:</p> <ul style="list-style-type: none"> - Sedative - Anticonvulsant - Antibiotic - Anti-inflammatory 	<p>CAS: 521-35-7 Empirical Formula: $C_{21}H_{26}O_2$ Molecular Weight: 310.43 g/mol Melting Point: 76–77 °C log P: 6.23 (octanol/water)</p> <p>Solubilities:</p> <p>Water: insoluble Ethanol: soluble Chloroform: soluble Hexane: soluble</p>
<p>(-)-Δ^9-trans-Tetrahydrocannabinolic Acid THCA</p>  <p>Main pharmacological characteristics:</p> <ul style="list-style-type: none"> - Antibacterial - Antibiotic 	<p>CAS: 23978-85-0 Empirical formula: $C_{22}H_{30}O_4$ Molecular weight: 358 g/mol Melting point: n/a (decomposition/ decarboxylation of THCA to THC at about 125-150°C)</p> <p>Solubilities:</p> <p>Water: insoluble Ethanol: soluble Chloroform: soluble Hexane: soluble</p>	<p>Cannabidiol CBD</p>  <p>Main pharmacological characteristics:</p> <ul style="list-style-type: none"> - Anxiolytic - Antipsychotic - Analgesic - Anti-inflammatory - Antispasmodic 	<p>CAS: 13956-29-1 Empirical formula: $C_{21}H_{30}O_2$ Molecular weight: 314.46 g/mol Melting point: 66–67 °C log P: 5.79 (octanol/water)</p> <p>Solubilities:</p> <p>Water: insoluble Ethanol: soluble Chloroform: soluble Hexane: soluble</p>

Proposed Action of Cannabis for different symptom.

THC

- Eases pain esp. in cancer
- Nausea vomiting
- Sleep disorders
- Mood disorders
- Relaxation คลายเครียด
- Suppress muscle spasm
- Reduce wasting

CBD

- Reduce dravet seizure
- Kill breast cancer cells
มะเร็ง
- Stop inflammation
- Anti oxidant
- Anti psychotic
- Increase appetite
- Change in weight

Thank you

“ **ตอนนี้ชักเจนว่า กัญชา**

อันตรายน้อยกว่า สุรา และ บุหรี่

ทุกวันนี้เราปล่อยให้สุราและบุหรี่ไปผ่านอยู่ในสังคม

เกิดโรคต่างมากมาย **โดยถูกกฎหมาย!!**

..ขณะที่เราไปกีดกันสมุนไพร

ซึ่งมันมีค่าในการดูแลผู้ป่วย..”

ดร.นพ. ธีวชัย กมลธรรม