Dr Ben Jansen

General Practitioner

Sports Doctor

Bundall Medical Centre

Gold Coast

Saturday, June 10, 2017

(Room 1)

16:30 - 17:25 WS #169: Medicinal Use of Cannabis

17:35 - 18:30 WS #181: Medicinal Use of Cannabis (Repeated)

Medicinal Cannabis 101

Dr Ben Jansen
Director @ Burleigh Heads Cannabis
FRNZCGP FRACGP FRCUCP

Medicinal Cannabis 101

Medicinal Cannabis 101

Medicinal Cannabis 101

BHC

BURLEIGHHEADSQLD

Take Home Messages

- Medicinal Cannabis does not need to get the patient “high” / neuropsychologically altered
- Start low and titrate dose to effect: THC 1mg
- No direct mortality from cannabis use
- CBD, among other cannabinoids, modulate THC effects
- The non-psychoactive natural raw acid forms of the cannabinoids are being used for CB2 reception modulation and preventing oxidative stress (among other effects)

Public Opinion On Regulation?

- **Prohibition**
- **Medication Restricted**
- **Medication Open**
- **Recreational Use* (still requires a level of quality and control for sale)**

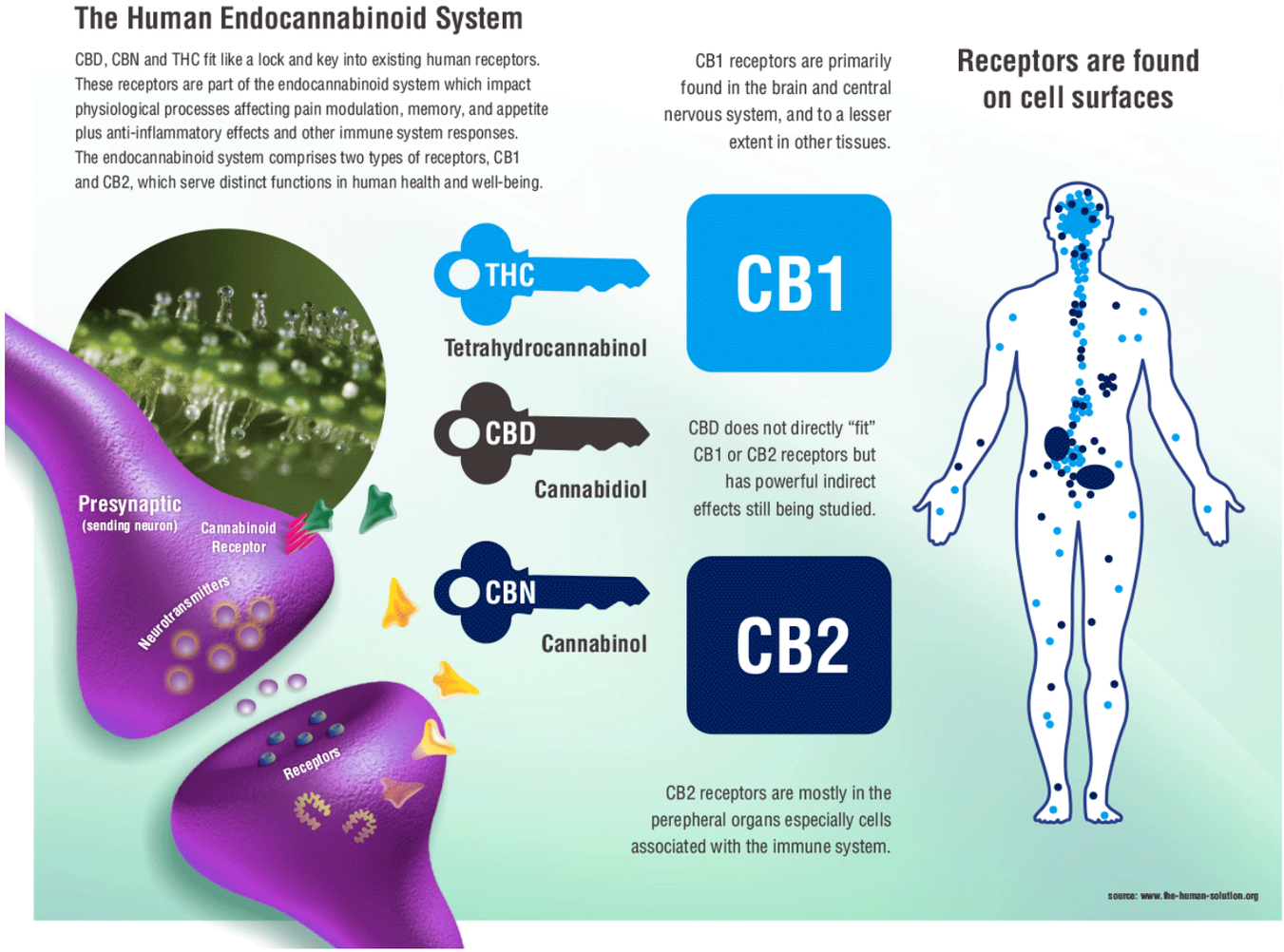
PubMed search 2017/4/1

- 31945 results for Cannabis, or Marijuana, or THC, or CBD
- Compared to 23924 for Paracetamol, or Acetaminophen
- Compared to 7511 for Metoprolol
- Compared to 2598 for Ramipril

Mortality

- **69000+ Opioid deaths estimated Worldwide in 2014 by the WHO.**
- **22598 deaths from Opioid Pain Relievers in the USA 2015.** National Center on Health Statistics, CDC WONDER
- **56,000 emergency room visits and 26,000 hospitalizations yearly from Paracetamol, and 458 deaths in the USA.** Nourjah P et al. Pharmacoepidemiol Drug Saf. 2006 Jun;15(6):398-405.
- **3,200 deaths annually as a result of NSAID-induced GI bleeding in the USA.** Tarone RE et al. Am J Ther. 2004;11(1):17-25.
- **Zero deaths from Cannabis, ever.** Dr Lester Grinspoon MD, Professor Emeritus, Harvard Medical School.

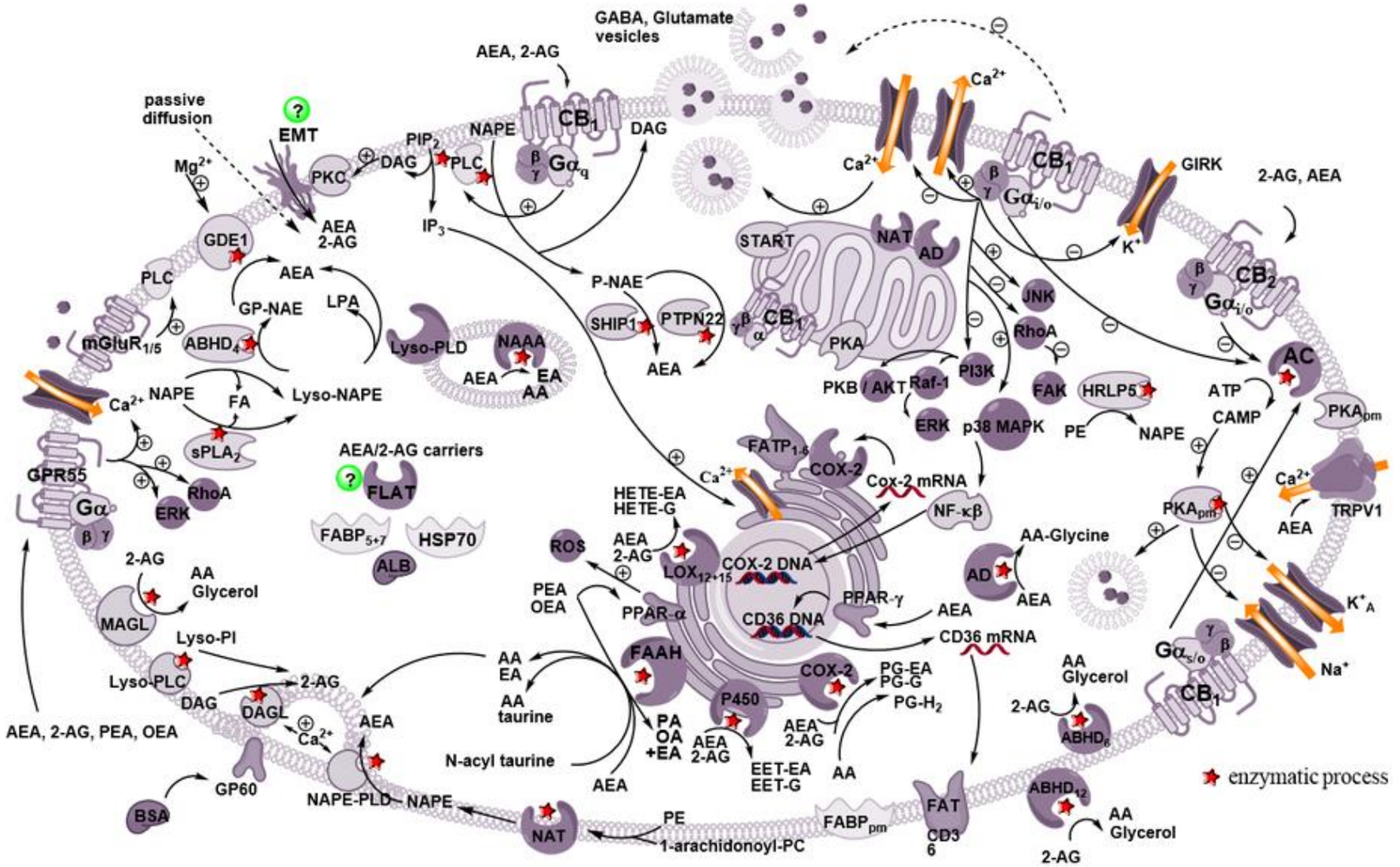
Endocannabinoid System



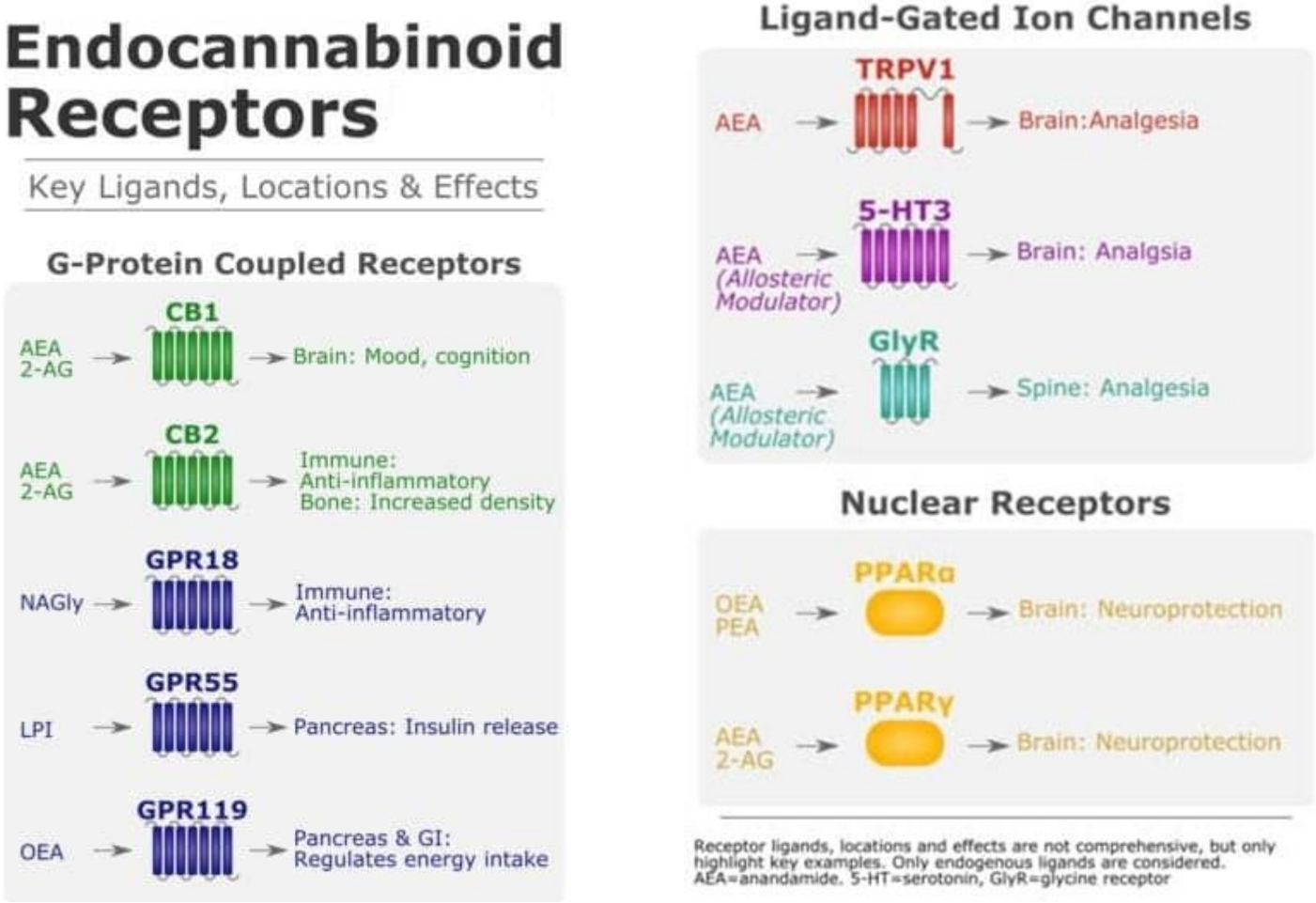
Endocannabinoid System

- **“The Bodies Own Cannabinoid System”**
- **Named because it was unknown until the effects of THC were being investigated**
- **Mostly cell membrane G protein-coupled receptors**
- **Related to homeostasis, memory, immune function, ….**

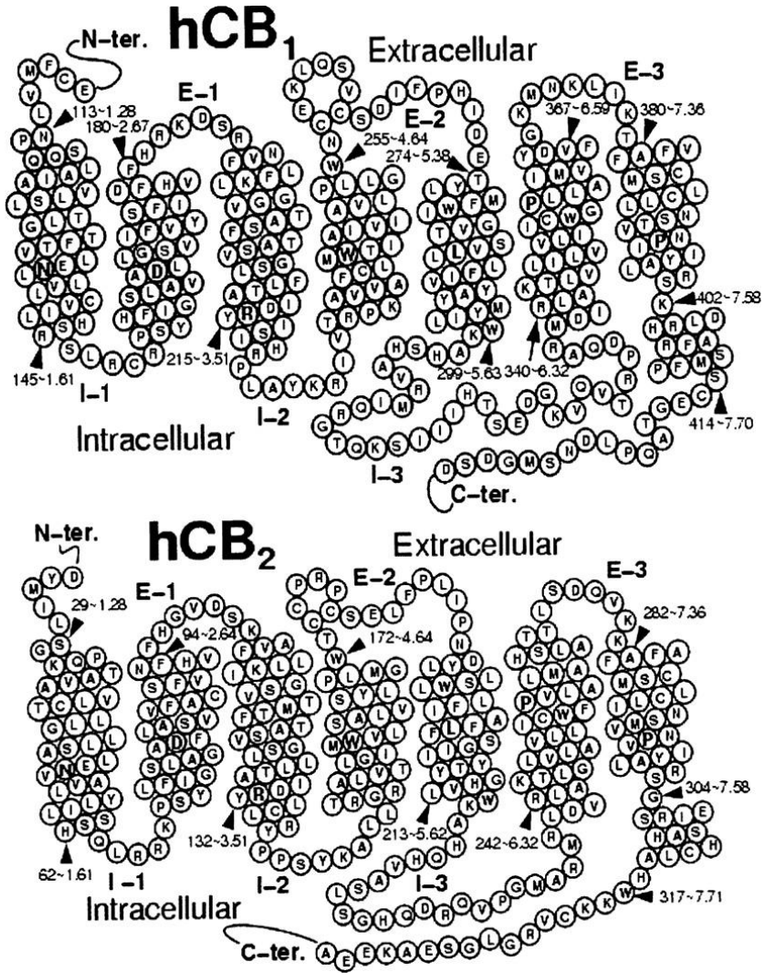
Endocannabinoid System



Endocannabinoid System – Receptors



Endocannabinoid System – CB1 + CB2



Reggio PH. Endocannabinoid Binding to the Cannabinoid Receptors: What Is Known and What Remains Unknown. Current medicinal chemistry. 2010;17(14):1468-1486.

Endocannabinoid System – CB1 receptors

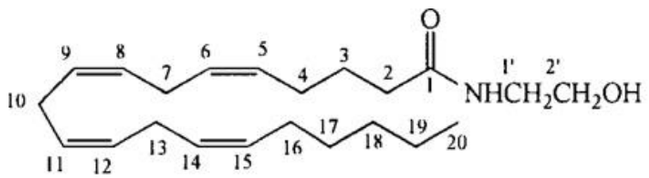
- **Two primary endocannabinoid receptors have been identified: CB1, first cloned in 1990; and CB2, cloned in 1993.**

- **CB1 receptors are found predominantly in the brain and nervous system working as a down-regulator, presumably to control neuron over-activity.**
- **CB1 receptors bind the endocannabinoid ligand (binding molecule), Anandamide (N-arachidonoylethanolamide, AEA), as well as its mimetic phytocannabinoid, THC.**
- **CB1 agonists affect processes involved in behaviour, mood and anxiety.**
- **CB1 receptors are critical for the regulation of the body's signalling of stress responses.** **Parker L. Cannabinoids and the Brain. Cambridge, MA; The MIT Press (2017).**

Endocannabinoid System – CB2 receptors

- CB2 receptors are found immune system, microglial cells, GI tract, peripheral nervous system...
- The other main endocannabinoid is 2-Arachidonoylglycerol (2-AG) which is active at both cannabinoid receptors, along with its own mimetic phytocannabinoid, CBD.
- 2-AG and CBD are involved in the regulation of appetite, immune system functions, pain management, and homeostasis.

Endocannabinoid System – Endogenous ECs



Anandamide

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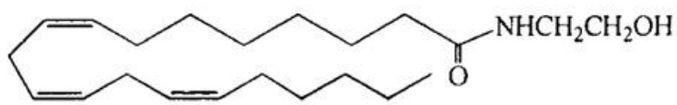
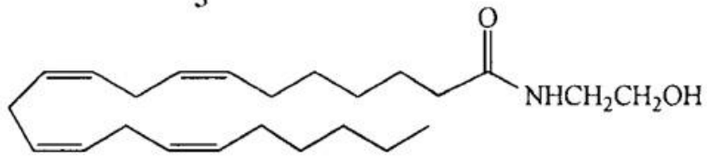


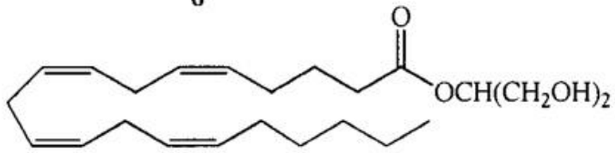
N-homo-gamma-linolenoyl-ethanolamine

6



N-docosotetraenoyl-ethanolamine

7



2-AG

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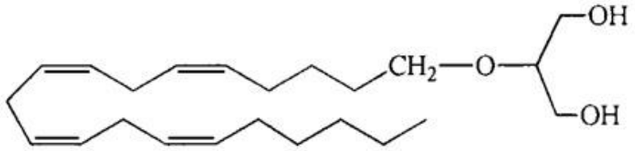

Noladin Ether

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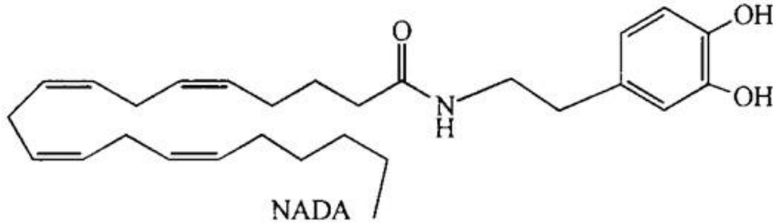

NADA

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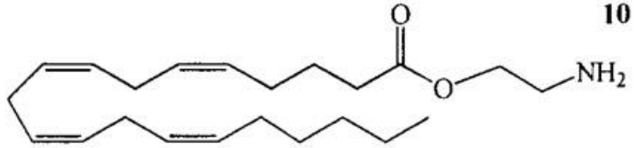


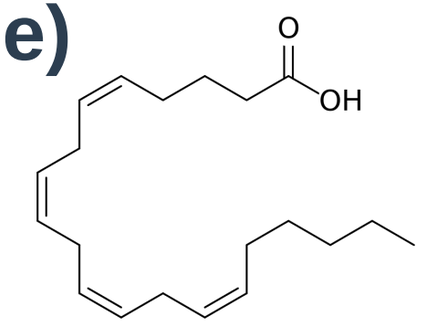
Virodhamine

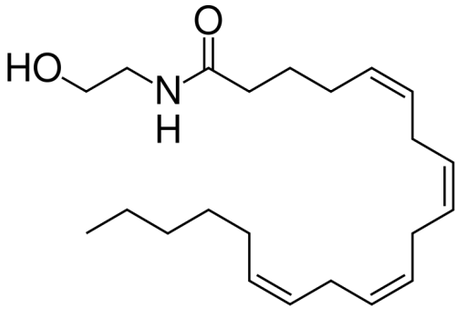
11

Reggio PH. Endocannabinoid Binding to the Cannabinoid Receptors: What Is Known and What Remains Unknown. Current medicinal chemistry. 2010;17(14):1468-1486.

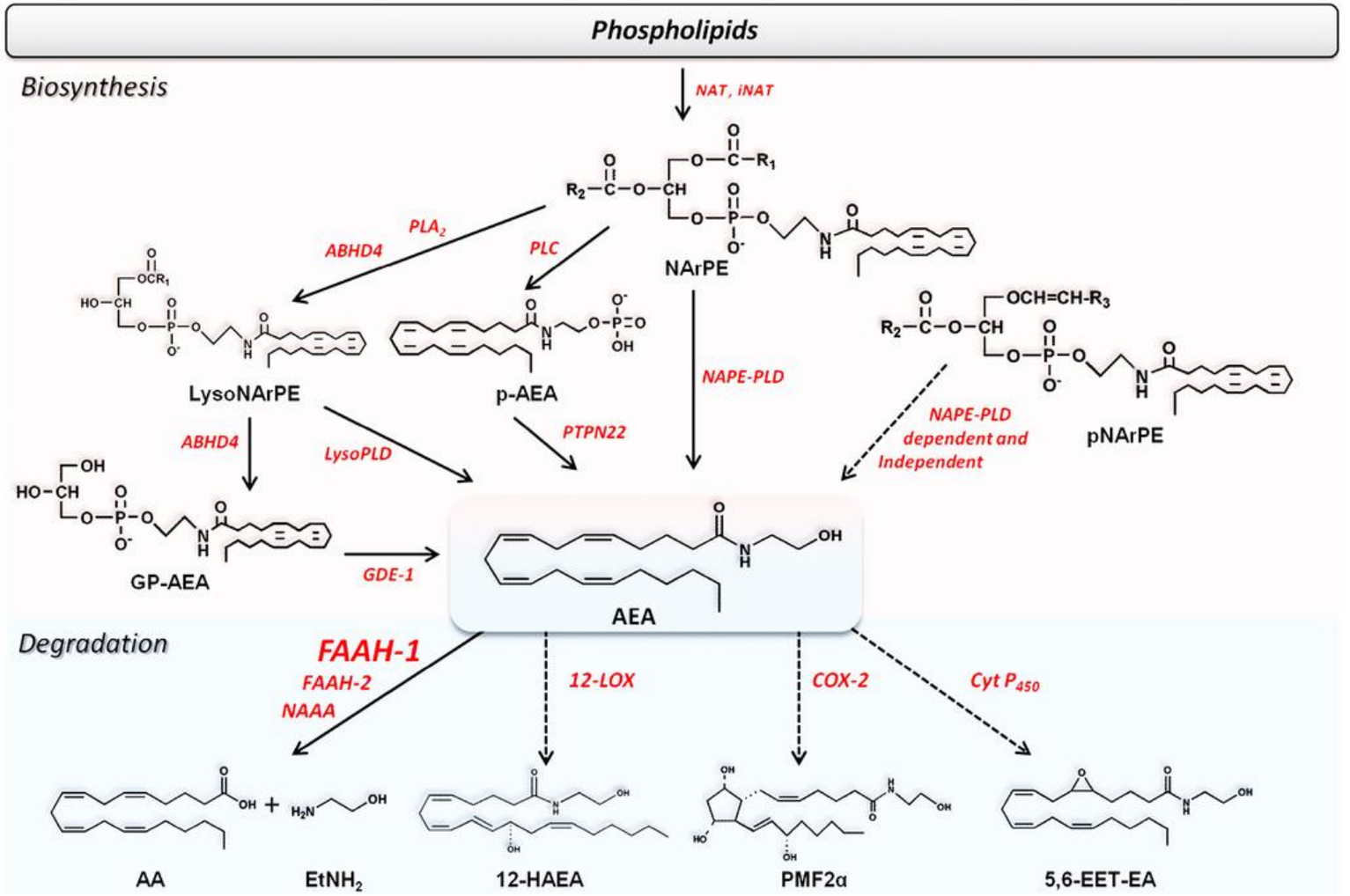
Endocannabinoid System - Anandamide

- **Named from the Sanskrit word “ananda” meaning “supreme joy”** (Devane et al 1992)
- **Binds to CB1, CB2, GPR55, GPR119, GPR18, TRPV1**
- **Abundant hippocampus endocannabinoid**
- **Produced on demand from ethanolamide addition to arachidonic acid* (no vesicle storage)**



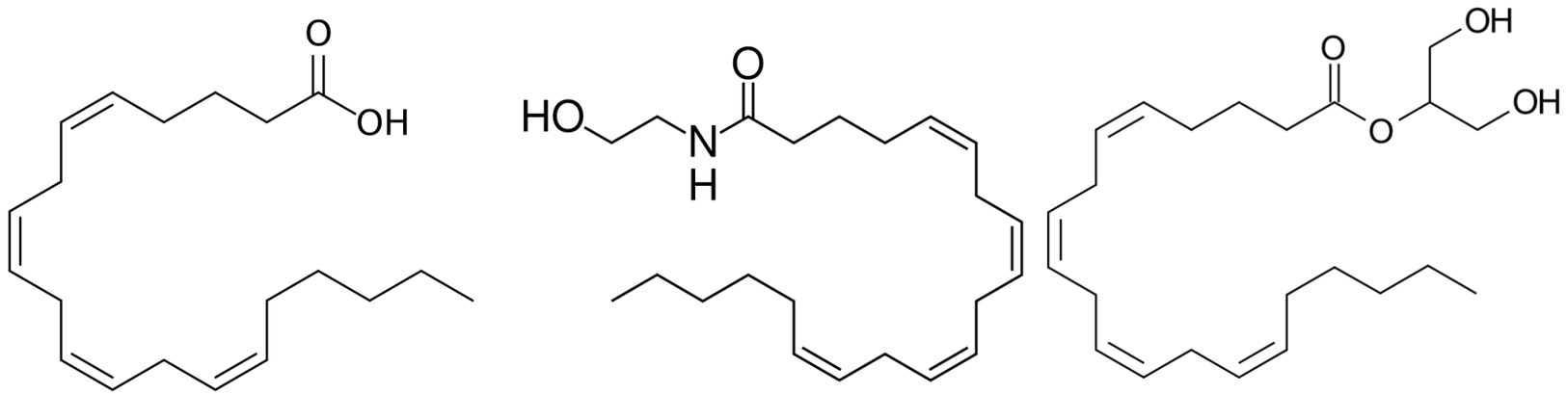


Endocannabinoid System - Anandamide



Endocannabinoid System - 2-AG

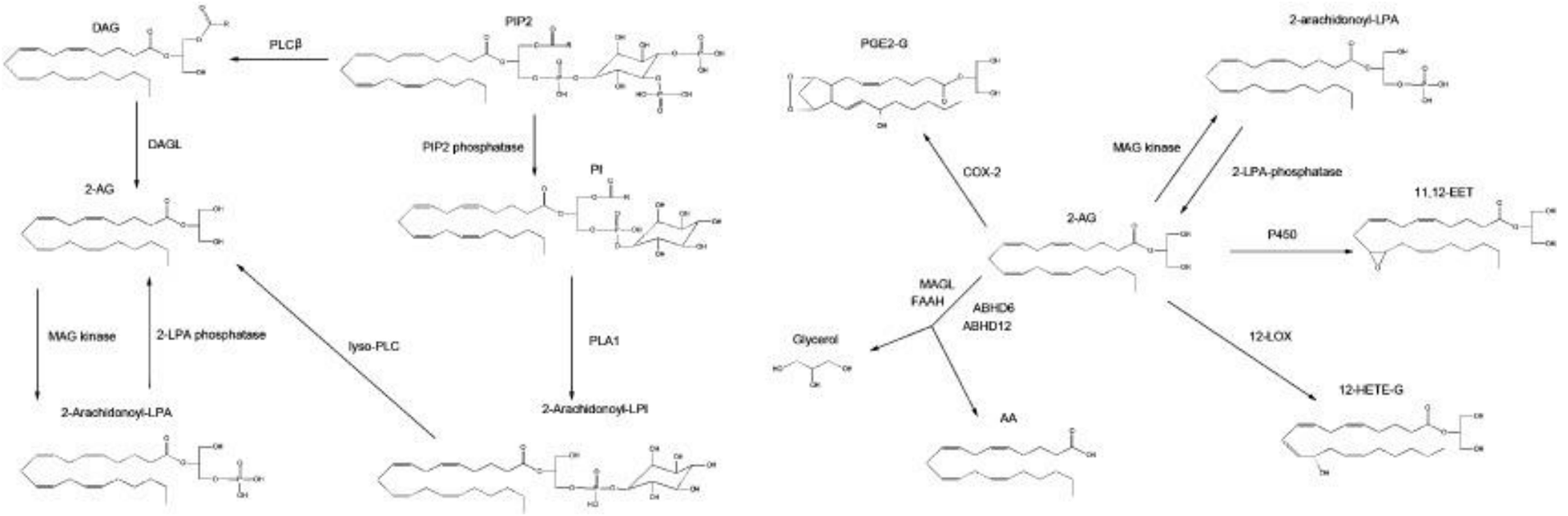
- 2-arachidonoyl glycerol described first in 1995.
- Full agonist at CB1 and CB2. Does not bind TRPV1.
- The most abundant endocannabinoid.
- Found in human breast milk.



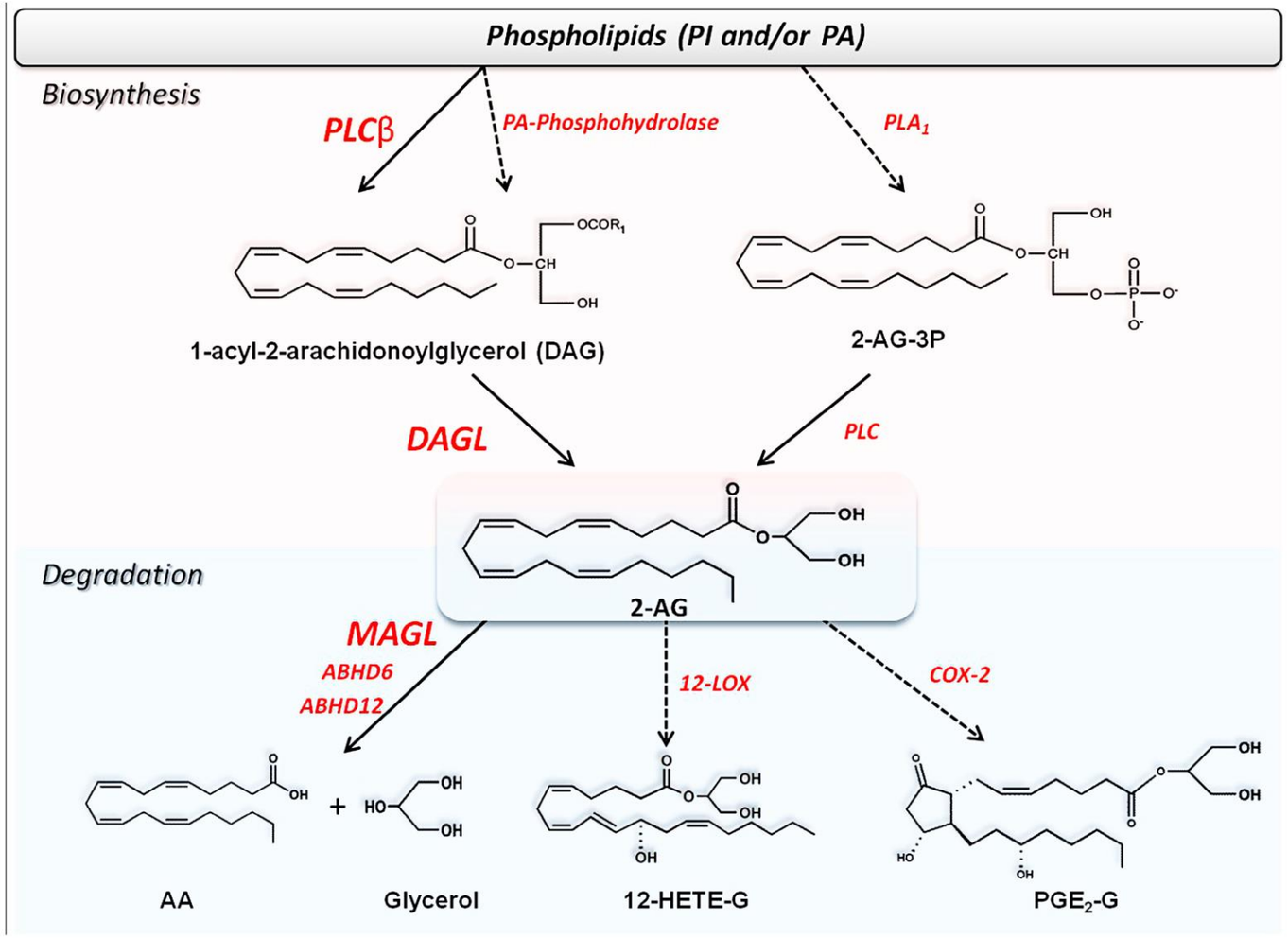
Endocannabinoid System – 2-AG

- 2-AG is not stored, but is synthesized on demand from arachidonic acid-containing diacylglycerol (DAG).
- DAGLα is the Ca2+ or metabotropic receptor dependent enzyme that mostly, if not uniquely, initiates this signal (Yoshino H et al. J Physiol 2011; 589: 4857–84).
- Release in neural CB1 sites is locally mediated, and effects are short lived due to rapid hydroxylation (MAGL for 2-AG, FAAH for AEA) and rapid reuptake.

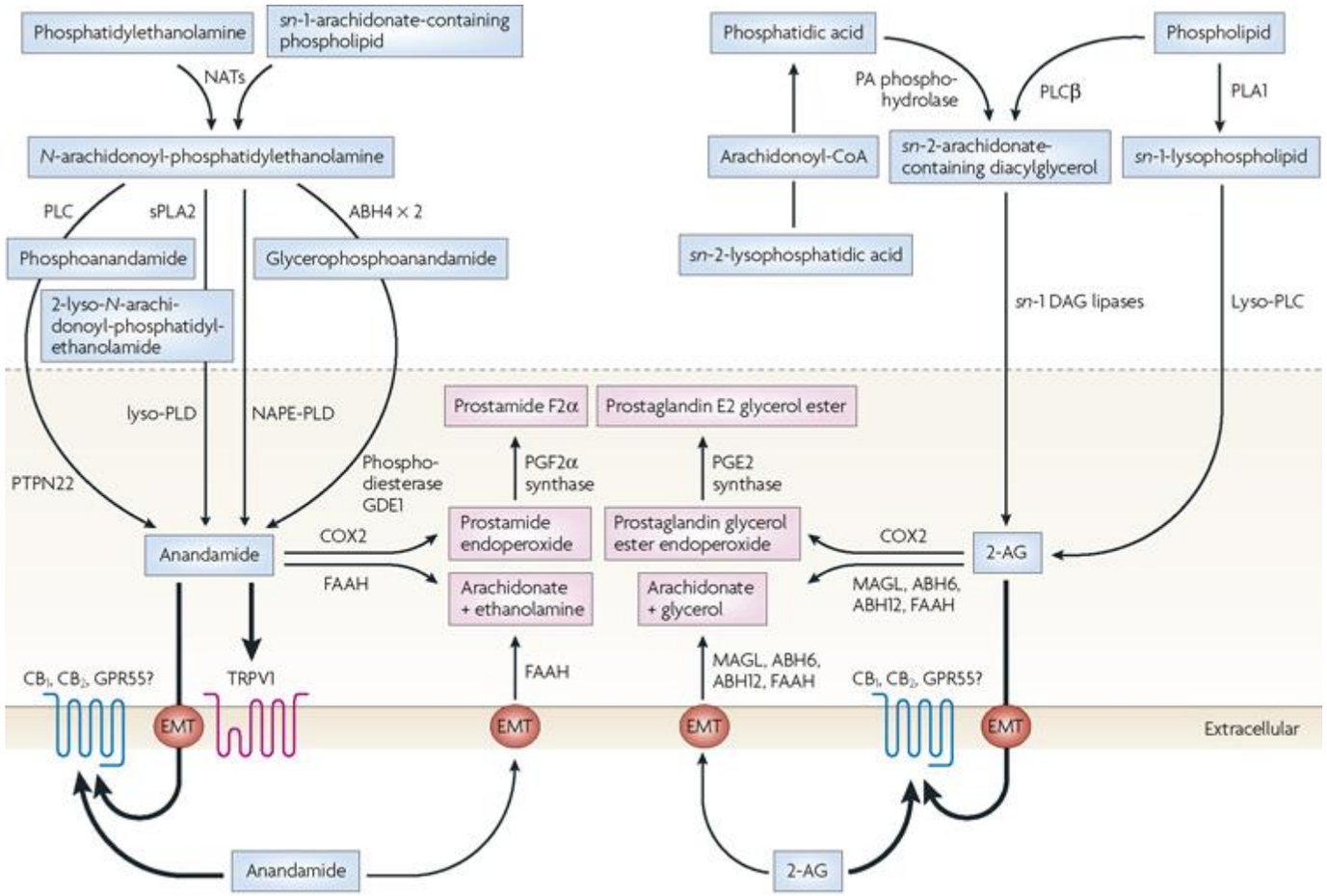
Endocannabinoid System – 2-AG



Endocannabinoid System – 2-AG



Endocannabinoid System – 2-AG



Nature Reviews | Drug Discovery

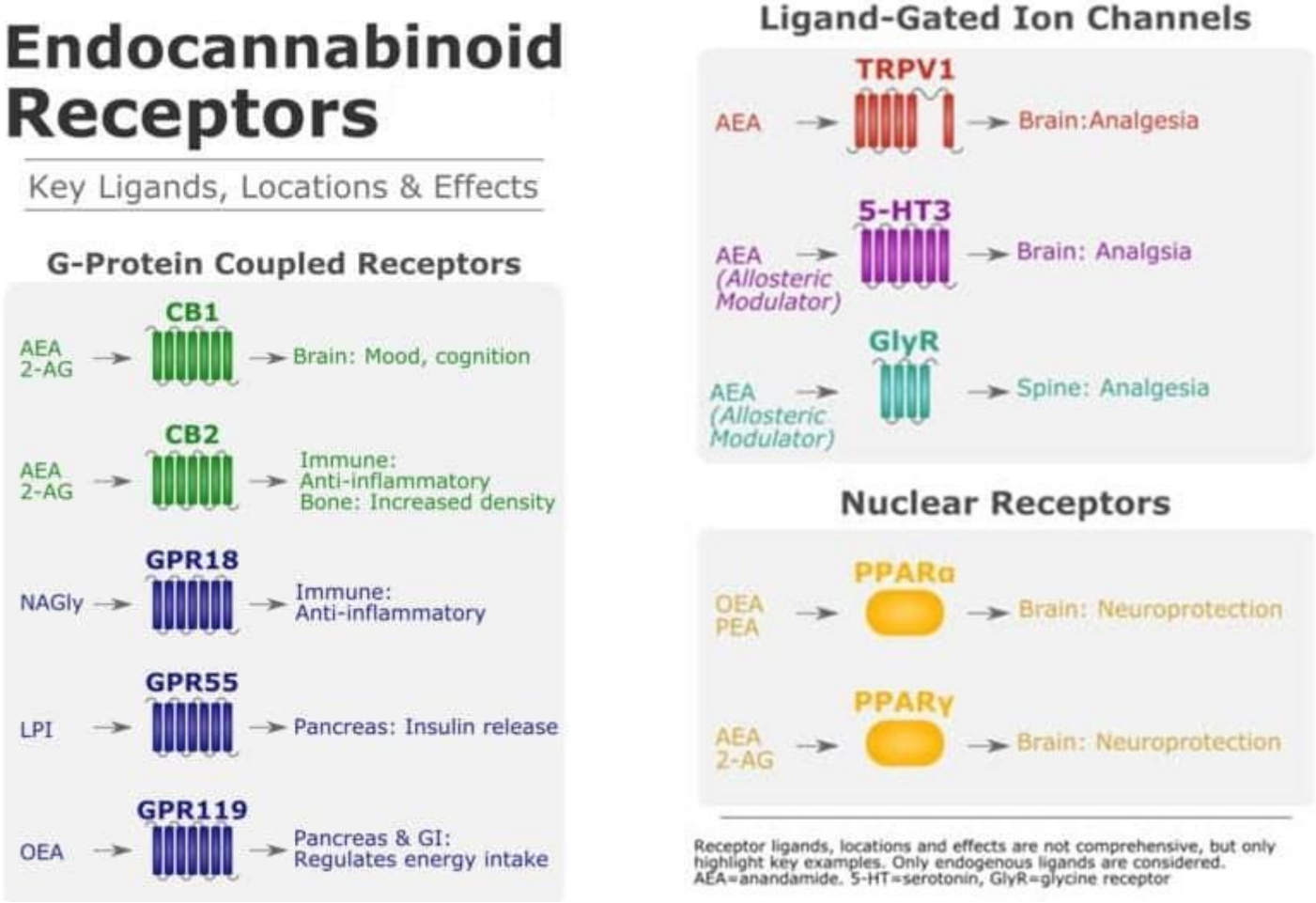
Endocannabinoid System – Other receptors

- GPR18 > Main ligand NAGly – lowers BP, immune effects incl. chemoattractant for immune cells.
- GPR55 > LPI – multisystem effects, lowers BP, anti-inflammatory, analgesic, energy homeostasis, neuroprotective.
- GPR119 > OEA - regulation of energy and metabolism.
- TRPV1 > AEA – analgesia and pain perception.

Endocannabinoid System – Other receptors

- Serotonin Receptors > AEA allosteric binding - nausea and vomiting, neuropathic analgesic.
- Glycine Receptors (GlyRs) > AEA allosteric binding - analgesia
- Peroxisome Proliferator-Activated Receptors (PPARs) > OEA and PEA - PPARs regulate cellular functions in almost every tissue, neuroprotection. PPARs reside within the cell and can directly bind to DNA sequences and change transcription of targeted genes.

Endocannabinoid System – Receptors



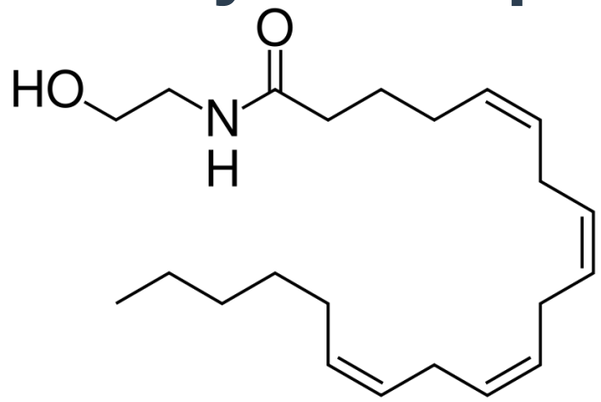
TPRV1 receptor

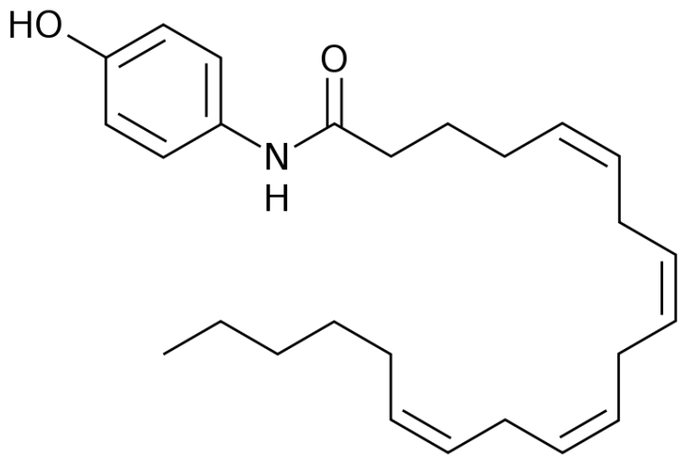
Aka Capsaicin receptor & the Vanilloid receptor 1 (Transient receptor potential cation channel subfamily V member 1)

- **Involved in heat sensation and pain detection, and also regulation of body temperature**
- **Agonists possibly cause down regulation eg Capsaicin cream**
- **Cannabidiol is an agonist**

Paracetamol and the EC system

- **Paracetamol (or acetaminophen for the yanks in the audience) is a COX-2 inhibitor, but also…**
- **Paracetamol is metabolically combined with arachidonic acid by FAAH to form AM404 (N-arachidonoylaminophenol):**

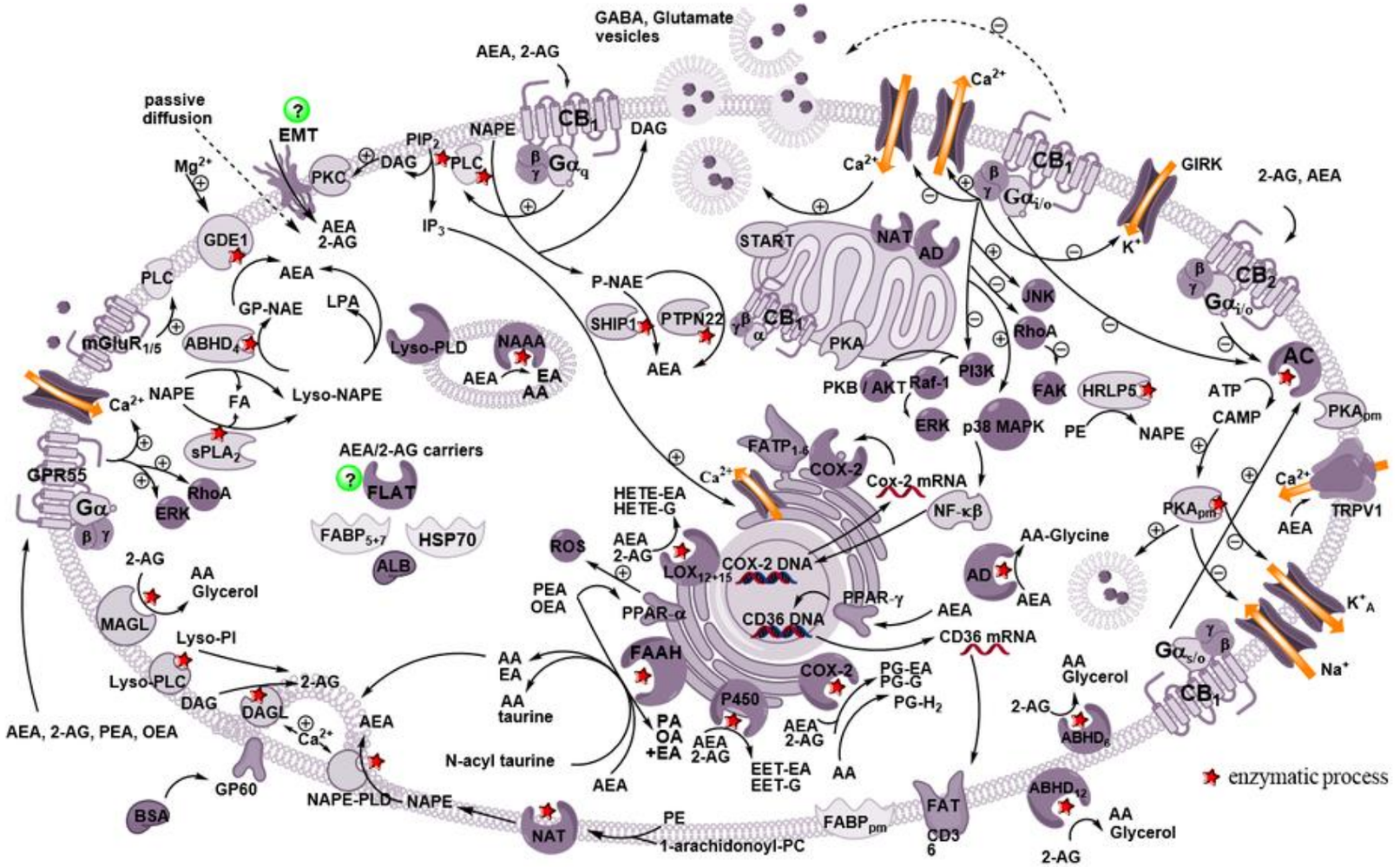




Paracetamol and the EC system

- AM404 a potent agonist at the TRPV1 vanilloid receptor, a weak agonist at both CB1 and CB2 receptors, and an inhibitor of anandamide reuptake
- As a result, anandamide levels in the body and brain are elevated
- In this fashion, paracetamol acts as a pro-drug for an endocannabinoid metabolite

Endocannabinoid System



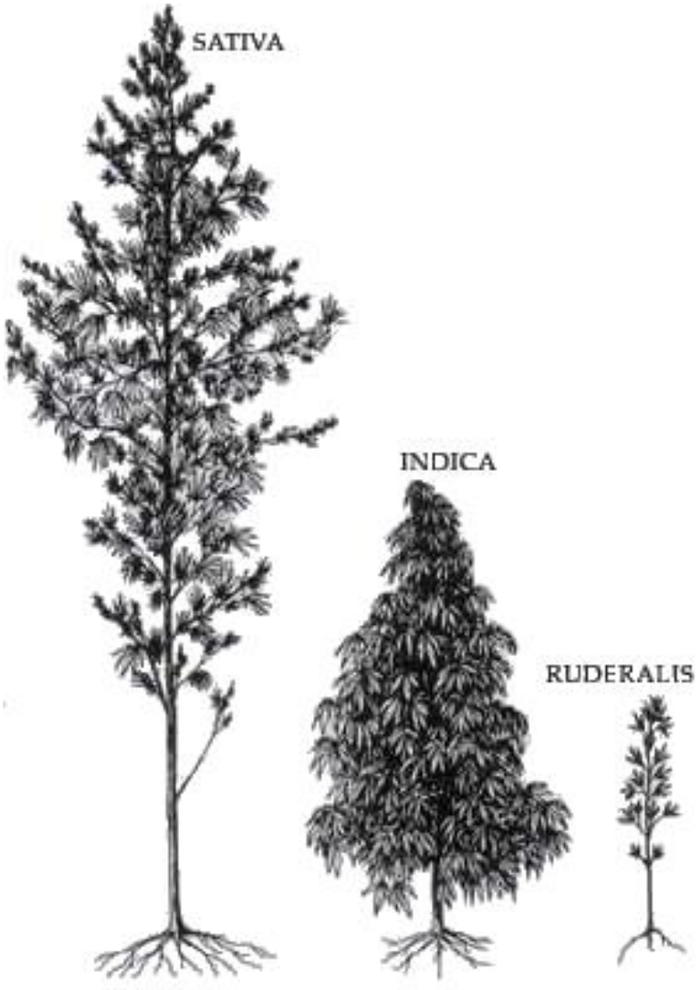
CEDS – Clinical Endocannabinoid Def Syn

- **ECS homeostatic roles have been summarized as “relax, eat, sleep, forget, and protect.”**
- **Suboptimal ECS functioning considerations: migraine, fibromyalgia, irritable bowel syndrome, “failure to thrive” syndrome, depressive illnesses, uncompensated schizophrenia, multiple sclerosis, Huntington's, uncompensated Parkinson's, uncompensated anorexia, and chronic motion sickness.**

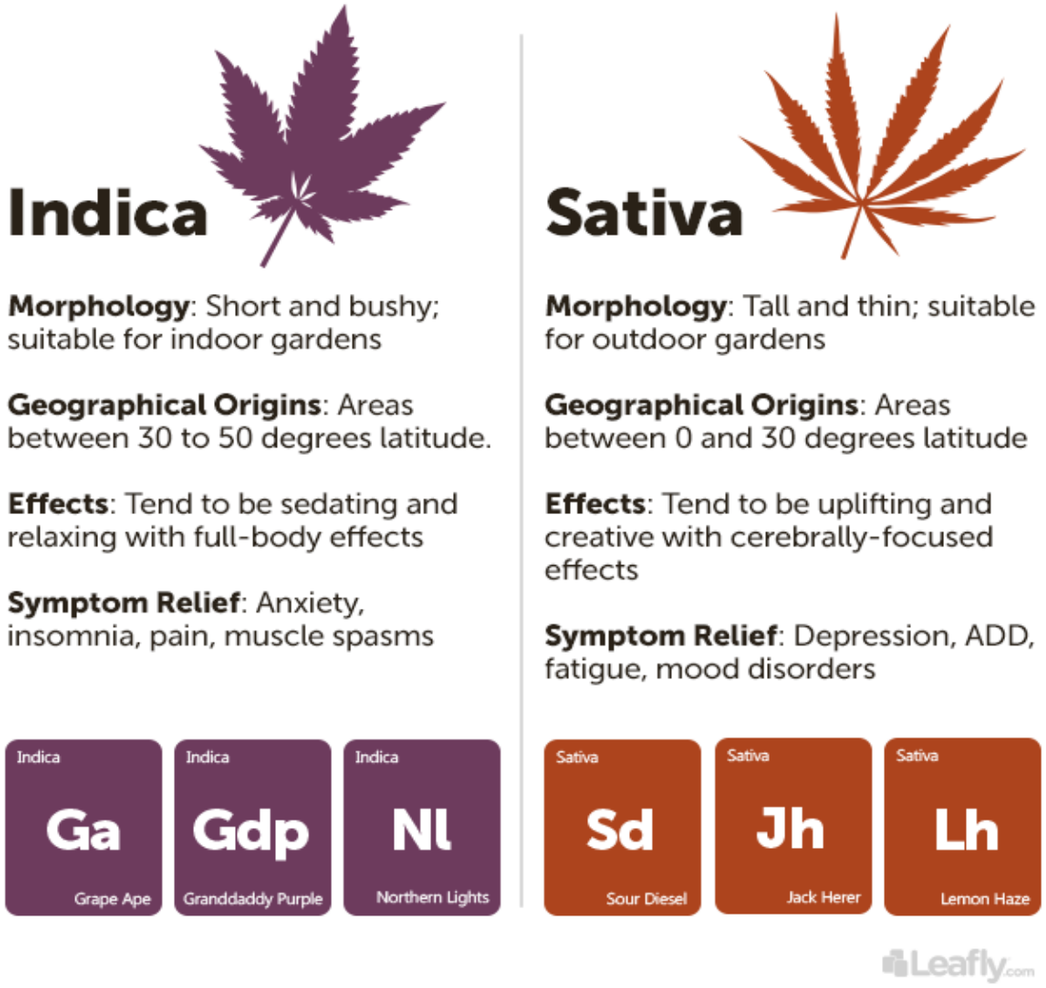
- **Correcting CEDS may be accomplished via at least three molecular mechanisms:**
  - 1. Augmenting Endocannabinoid ligand biosynthesis;
  - 2. Decreasing Endocannabinoid ligand degradation;
  - 3. Augmenting or decreasing receptor density or function.

- **McPartland JM, Guy GW, Di Marzo V. Care and Feeding of the Endocannabinoid System: A Systematic Review of Potential Clinical Interventions that Upregulate the Endocannabinoid System. Romanovsky AA, ed. PLoS ONE. 2014;9(3):e89566. doi:10.1371/journal.pone.0089566.**

Cannabis Plants



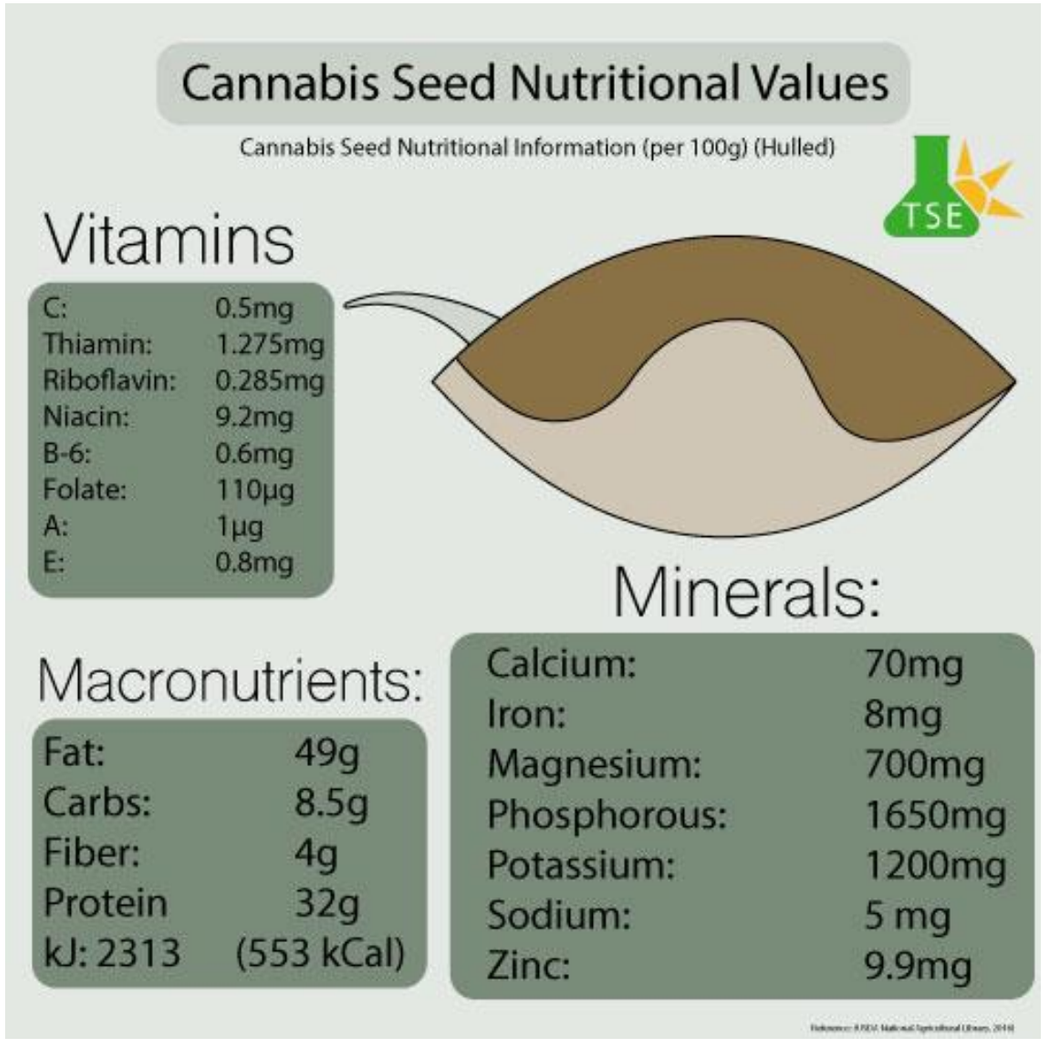
Cannabis Plants – Indica, Sativa, and Hybrids



Cannabis Components

- 400+ molecules in raw Cannabis
- 100+ Terpenes (volatile unsaturated hydrocarbons found in the essential oils)
- 112+ different Cannabinoids
- Cannabinoids in acid forms
- Fibre
- PUFA’s, phytosterols, vit E, G+C Linoleic Acid, omega 3’s + 6’s, folate, Mg, Fe, Zn, Protein

Hemp Seeds


Cannabis Seed Nutritional Values
Cannabis Seed Nutritional Information (per 100g) (Hulled)
TSE
Vitamins
C: 0.5mg
Thiamin: 1.275mg
Riboflavin: 0.285mg
Niacin: 9.2mg
B-6: 0.6mg
Folate: 110µg
A: 1µg
E: 0.8mg
Minerals:
Calcium: 70mg
Iron: 8mg
Magnesium: 700mg
Phosphorous: 1650mg
Potassium: 1200mg
Sodium: 5 mg
Zinc: 9.9mg
Macronutrients:
Fat: 49g
Carbs: 8.5g
Fiber: 4g
Protein 32g
kJ: 2313 (553 kCal)

Hemp Seeds

Shelled Hemp Seeds

Product Specification & Analysis per 100g

Calories	578-630 cal
Protein	31-33%
Carbohydrates	7-10%
Fat	46-50%
Ash	5-8%
Moisture	5-7%
Cholesterol	0%
Volatile Impurities	Traces (below USP requirements)
Standard Plate Count	Less than 25,000 CFU/g
Total Coliforms	Less than 1000 CFU/g
Fecal Coliforms	<2 CFU/g
Yeast & Mold	<1000 CFU/g
E.coli	Negative
Samonella	Negative
Clostridium Perfringens	Negative
Clostridium Species	Negative
Bacillus Cereus	Negative

Other:

Beta Carotene	11.4 IU/100g
pH value:	6.85
THC Content	none detected – limit of detection 4 ppm
Free Fatty Acids	0.5-2.0% (as Oleic acid)
Peroxide Value	0.4-2.0 meq/kg
Gluten	negative (<3ppm) – limit of detection 3

Nutrition Facts

Serving size: 100g

Amount per serving

Calories 600 Calories from Fat 440

	Daily Value*
Total Fat 49g	75%
Saturated Fat 4g	20%
Trans Fat 0g	
Polyunsaturated Fat 37g	
Monounsaturated Fat 5g	
Cholesterol 0mg	0%
Sodium 0mg	0%
Potassium 990mg	28%
Total Carbohydrate 7g	2%
Dietary fiber 3g	10%
Sugars 2g	
Protein 33g	

Vitamin A 0%	•	Vitamin C 0%	
Calcium 6%	•	Iron 70%	
Vitamin E 120%	•	Thiamine 110%	
Riboflavin 810%	•	Niacin 25%	
Vitamin B_6 0%	•	Phosphorus 130%	
Magnesium 140%	•	Zinc 60%	
Copper 90 %	•	Manganese 290%	

*Percent daily values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories	2,000	2,500
Total Fat	Less than	65g	80g
Saturated Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Potassium	Less than	3,500mg	3,500mg
Total carbohydrate		300g	375g
Dietary fiber		25g	30 g

Calories per gram:

Fat 9 • Carbohydrates 4 • Protein 4

Fatty Acid Profile per 100g of hulled hemp seed

Fatty Acid	Weight (g)
Myristic Acid	0.06
Palmitic Acid	3.01
Stearic Acid	1.05
Oleic Acid (Omega 9)	5.25
Linoleic Acid (Omega 6)	27.67
CLA	0.41
Arachidic Acid	0.35
Gamma Linolenic Acid	1.92
Linolenic Acid (Omega 3)	8.56
Stearidonic Acid	0.41
Behenic Acid	0.12

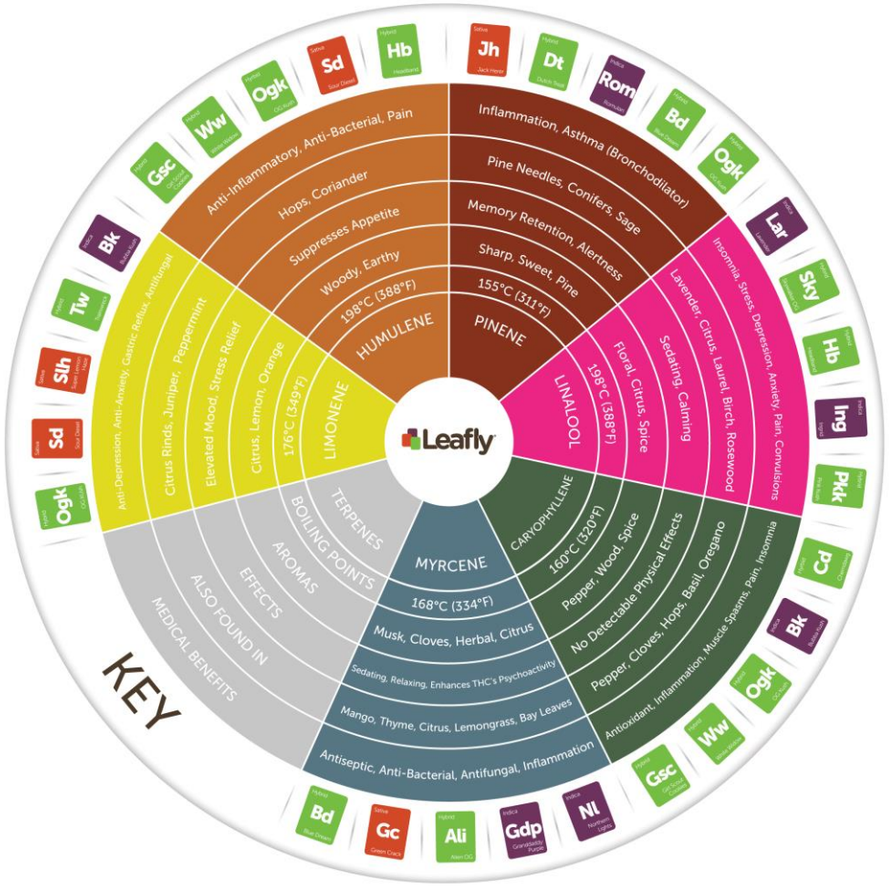
Amino Acid Profile per 100g of hulled hemp seed

Amino Acid	Weight (g)	Amino Acid	Weight (g)
Aspartic	3.09	Theronine	1.05
Serine	1.54	Glutamic	5.61
Proline	1.13	Glycine	1.35
Alanine	1.30	Cysteine	0.57
Valine	1.47	Methionine	0.75
Isoleucine	1.15	Leucine	2.04
Tyrosine	0.94	Phenylalanine	1.39
Histidine	0.82	Lysine	1.13
Arginine	3.58	Tryptophan	0.25

Protein Digestibility: 93%

PDCAAS: 0.65

Terpenes



References

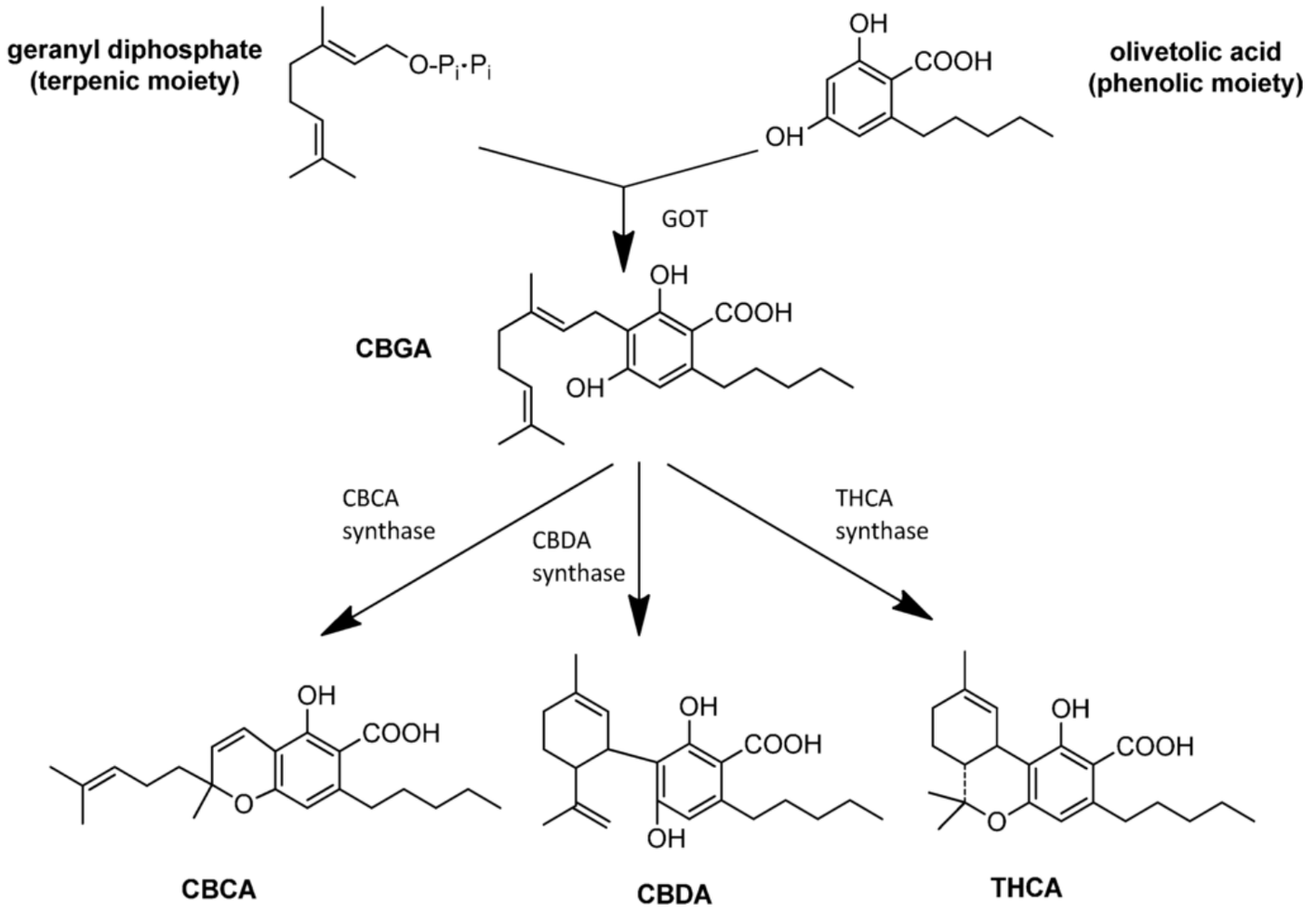
http://steephill.com/resources/cannabinoid-and-terpenoid-reference-guide/

http://sclabs.com/learn/terpenes.html

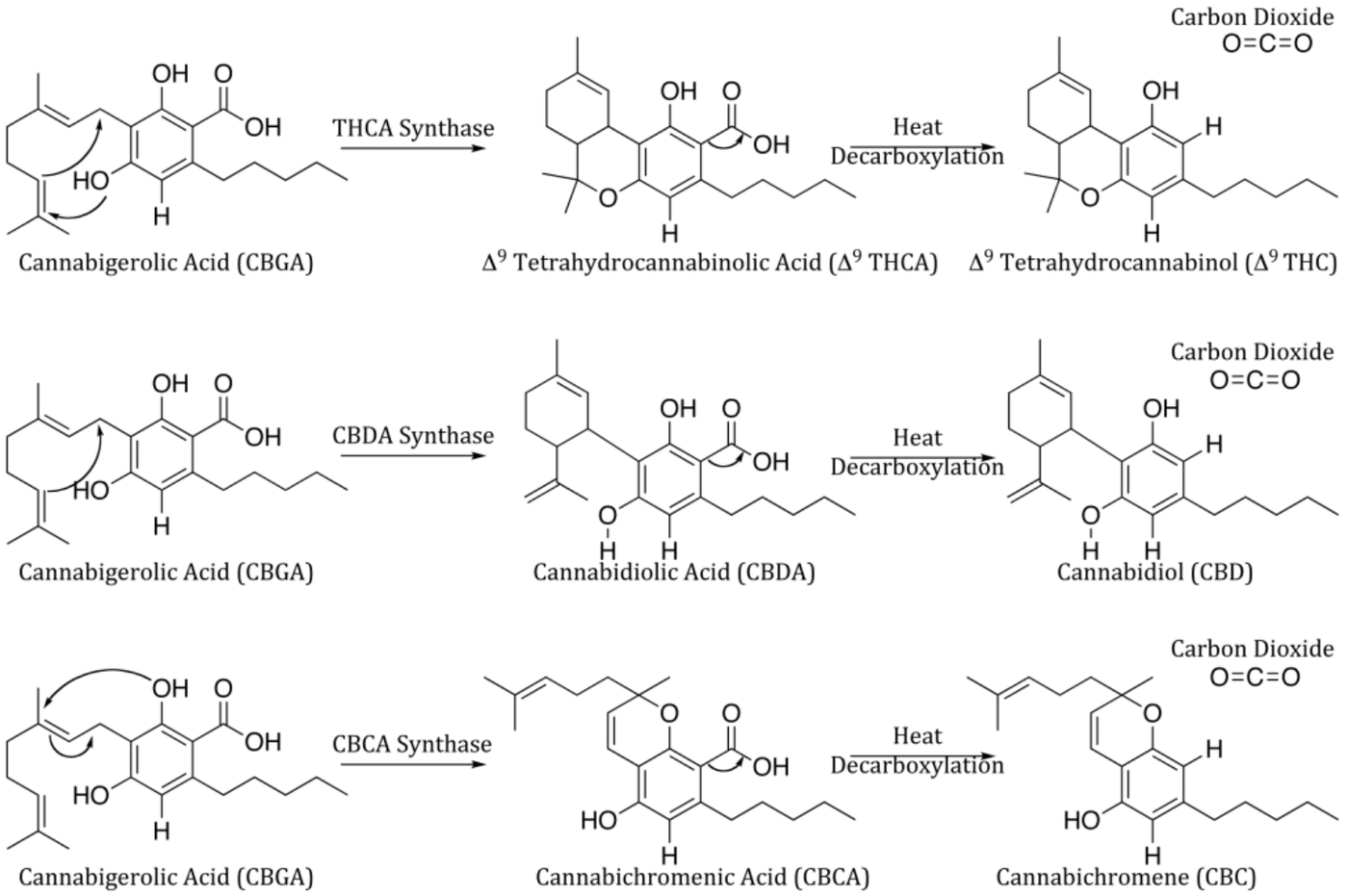
Phytocannabinoids

- CBG (Cannabigerol)
- CBC (Cannabichromene)
- CBL (Cannabicyclol)
- CBV (Cannabivarin)
- THCV (Tetrahydrocannabivarin)
- CBDV (Cannabidivarin)
- CBCV (Cannabichromevarin)
- CBGV (Cannabigerovarin)
- CBGM (Cannabigerol Monomethyl Ether)
- THC (Tetrahydrocannabinol)
- THCA (Tetrahydrocannbinolic acid)
- CBD (Cannabidiol)
- CBDA (Cannabidiolic Acid)

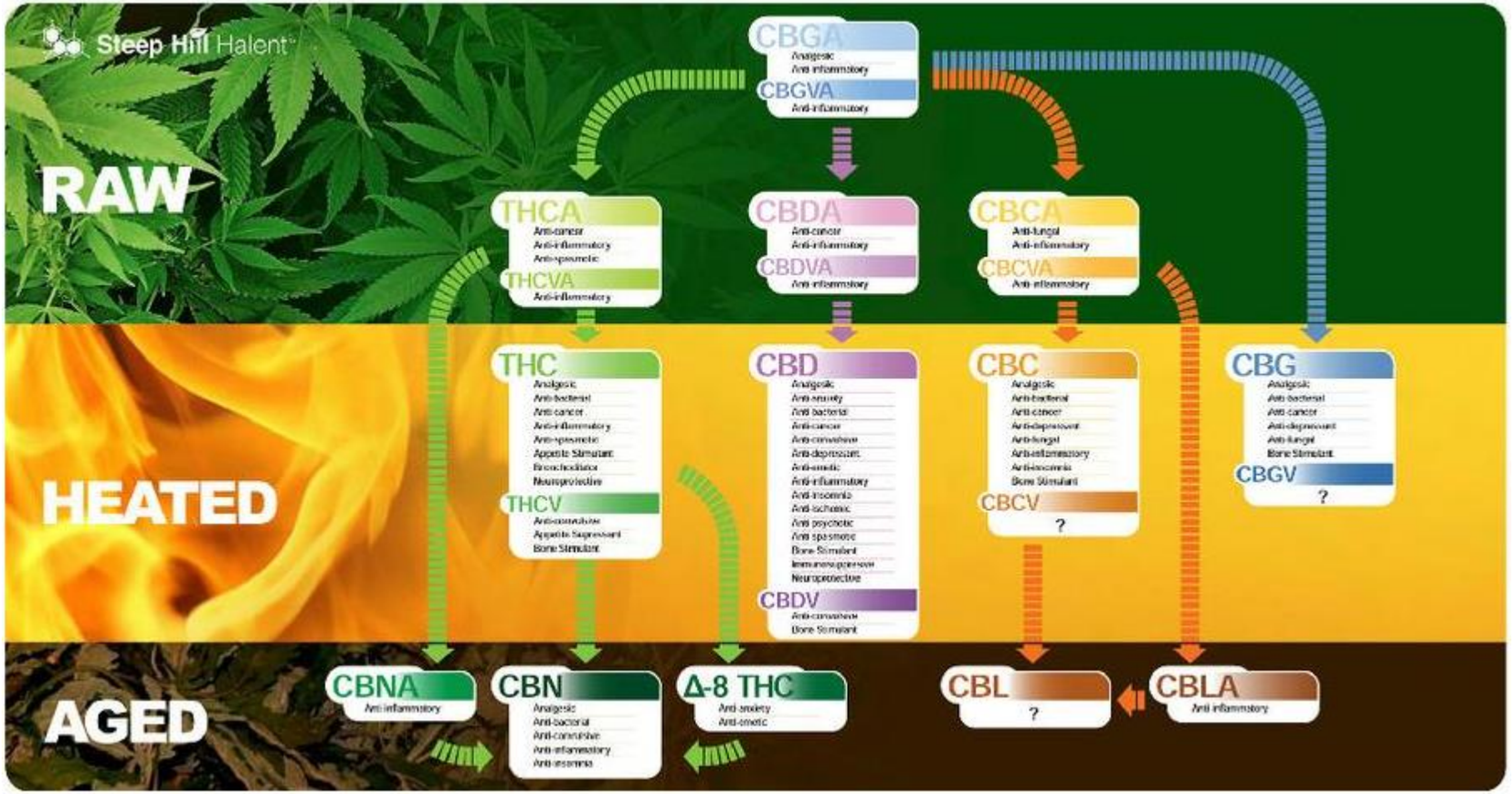
Cannabinoid Biosynthesis



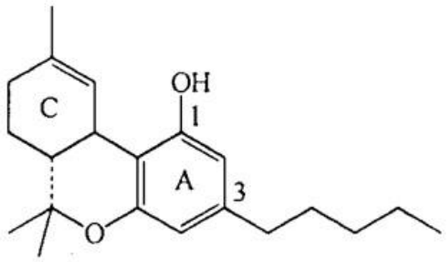
Cannabinoid Biosynthesis



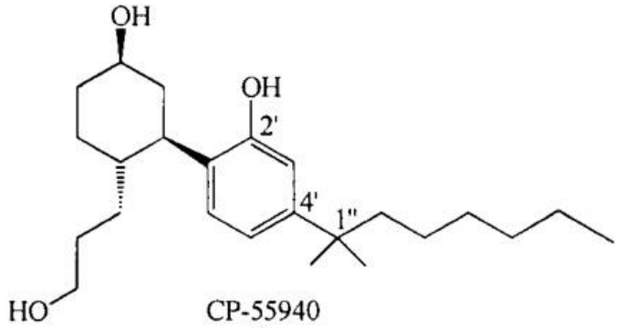
Cannabinoid Biosynthesis



THC and synthetics



Delta-9-THC
1



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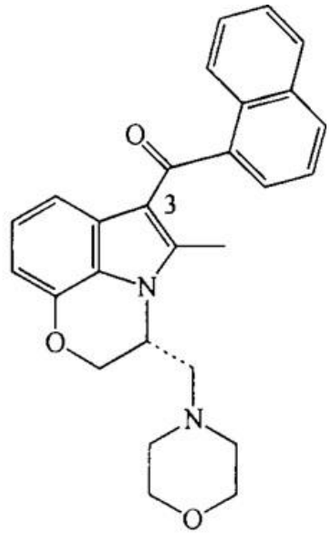

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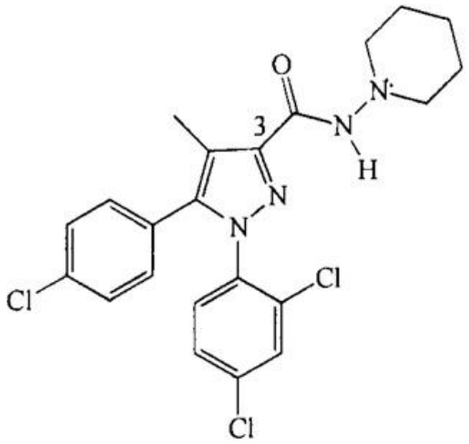

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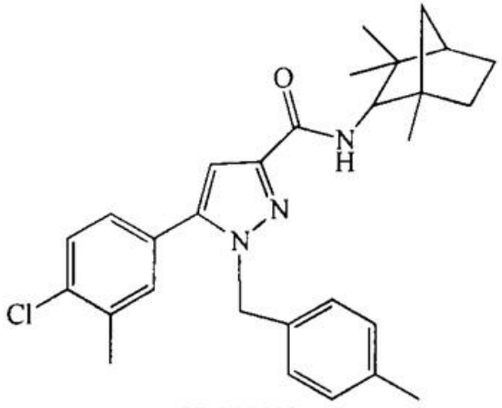

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Reggio PH. Endocannabinoid Binding to the Cannabinoid Receptors: What Is Known and What Remains Unknown. Current medicinal chemistry. 2010;17(14):1468-1486.

Cannabidiol – CBD

- **Does not get you “high”; Not Psychoactive.**
- **Low binding affinity for CB1 and CB2 receptors, but activates several non-cannabinoid receptors and ion channels.**
- **Delays the reuptake and breakdown of endogenous endocannabinoids (such as anandamide) – this is the entourage effect with other cannabinoids.**

Cannabidiol – CBD

- 5-HT1A serotonin receptor agonist (CBDA more of an agonist), with **antidepressant activity**.
- TRPV1 agonist, with **analgesic effects**.
- GPR55 antagonist, with **anti-osteoporosis and anticancer cell proliferation effects**.
- CBD's anti-inflammatory and anti-anxiety effects are in part attributable to its **inhibition of adenosine reuptake**. A1A and A2A adenosine receptors play significant roles in cardiovascular function, regulating myocardial oxygen consumption and coronary blood flow. **These receptors have broad anti-inflammatory effects throughout the body.**

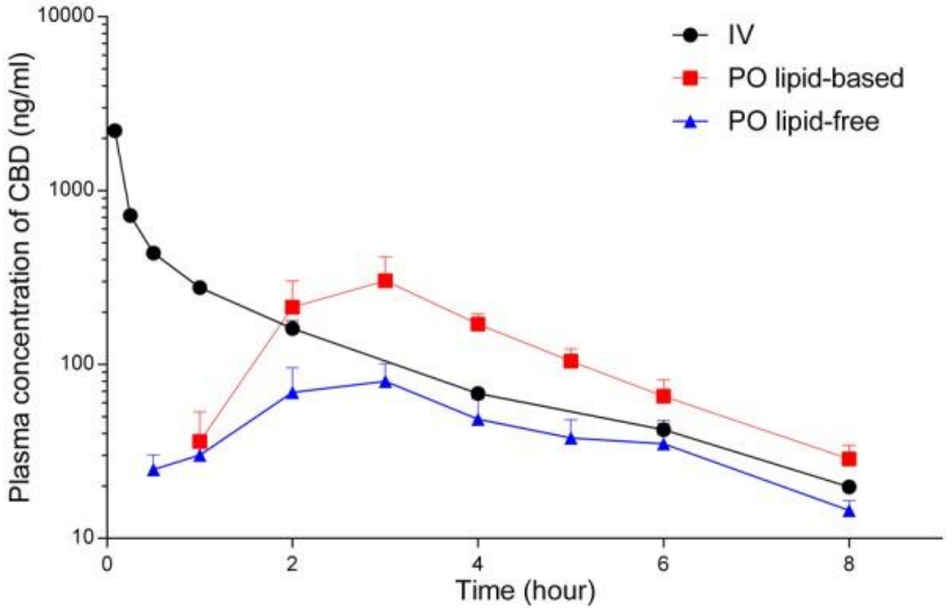
CBD Dose

- To decrease THC psychoactive effects: 1:1+ THC:CBD ratio
- To treat chronic pain: 2.5-20 mg CBD by mouth for an average of 25 days
- To treat epilepsy: 200-600 mg of CBD by mouth daily for up to 4.5 months
- To treat movement problems associated with Huntington’s disease: 10 mg per kilogram of CBD by mouth daily for six weeks
- To treat sleep disorders: 40-160 mg CBD by mouth
- To treat multiple sclerosis symptoms: Cannabis plant extracts containing 2.5-120 mg of a THC-CBD combination by mouth daily for 2-15 weeks
- To treat schizophrenia: 40-1,280 mg CBD by mouth daily for up to four weeks

CBD Bioavailability

- **Oral 10% > 20% with long-chain TG**
- **Inhalation 30%**

- **Zgair A, Wong JC, Lee JB, et al. Dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicines. American Journal of Translational Research. 2016;8(8):3448-3459.**



CBD Myocardial Protection

- **“Cannabidiol, a nonpsychoactive Cannabis constituent, protects against myocardial ischemic reperfusion injury”.** Durst et al. Am J of Physiology - Heart and Circ Physiology, 1 Dec 2007; 293 (6), H3602-H3607. DOI: 10.1152/ajpheart.00098.2007
- **The LAD coronary artery was transiently ligated for 30 min, and the rats were treated for 7 days with CBD (5 mg/kg ip) or placebo vehicle.**
- **Infarct size was reduced by 66% in CBD-treated animals.**

CBD Neuroprotection - US Patent US6630507

- **US Patent US6630507 - CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS (2003)** **Assignee: The United States of America as represented by the Department of Health and Human Services, Washington, DC (US)**
- **“This new found property makes Cannabinoids useful in the treatment and prophylaxis of a wide variety of oxidation associated diseases, such as ischemic, age-related, infammatory 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.”**

CBD Neuroprotection - US Patent US6630507

- **US Patent US6630507 - CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS (2003)** **Assignee: The United States of America as represented by the Department of Health and Human Services, Washington, DC (US)**
- **“Nonpsychoactive Cannabinoids, such as cannabidiol, are particularly advantageous to use because they avoid toxicity that is encountered with psychoactive Cannabinoids at high doses.”**

CBD Neuroprotection - US Patent US6630507

- **US Patent US6630507 - CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS (2003)** **Assignee: The United States of America as represented by the Department of Health and Human Services, Washington, DC (US)**
- **Example 7 “The middle cerebral artery of chloral hydrate anaesthetised rats was occluded by insertion of suture thread into it. The animals were allowed to recover from the anesthetic and move freely for a period of two hours. After this time the suture was removed under mild anesthetic and the animals allowed to recover for 48 hours.”**
- **“Infarct size was approximately halved in the animals treated with cannabidiol, which was also accompanied by a substantial improvement in the neurological status of the animal.”**

- **Dr Raphael Mechoulam**

Dr Raphael Mechoulam

- "Israeli scientists have been involved in cannabis preclinical research over 50 years, and clinicians have done clinical research and have treated patients with cannabis for over a decade. But we still have to learn and get additional experience, particularly in the clinic. However, with the vast knowledge already available, it should be possible to advance rapidly. I see at least two possible directions: CBD is a nontoxic molecule which does not seem to cause side effects. However, the doses needed are high. Thus, in schizophrenia, CBD has been assayed in the clinic with very positive results. But the doses needed are 800 mg/day due to low bioavailability."

- "They should be undertaken not only with the pure constituents but also in well-defined mixtures, previously evaluated in animal models and based on the possible 'entourage effect.'"

Δ9-Tetrahydrocannabinol - THC

- **THCA is not psychoactive, but heated to 120*c will turn into THC which is psychoactive.**
- **The LD50 values for Fischer rats treated orally with single doses of delta-9-THC and delta-8THC, and observed for 7 days, are 1910 mg/kg and 1980 mg/kg (for males) respectively and 860 mg/kg (for females).**
- **LD50 could not be determined in either rhesus monkeys or dogs as single oral doses of up to 9000 mg/kg of either delta-8- or delta-9-THC in dogs or monkeys were non-lethal. (Compare to Nicotine: for rats – 50 mg/kg, for humans – 0.5-1 mg/kg)** Thompson, G. R. et. al., 1973. Toxicol. Appl. Pharmacol. 25: 373-390.

Δ9-Tetrahydrocannabinol - THC

- THC is a partial agonist at CB1 > CB2 receptors.
- THC binding to CB1 pathways acts as a downregulator of those neurons.
- THC may act on some areas to increase endogenous endocannabinoid activity. Pertwee RG. Brit J of Phar, 2008. 153 (2): 199–215.
- THC is positive allosteric modulator of the μ- and δ-opioid receptors. Kathmann M et al. Naunyn Schmiedebergs Arch. Pharmacol, 2006 372 (5): 354–61.

THC Effects

- **Analgesic – Relieves pain.**
- **Anti-Emetic – Reduces vomiting and nausea.**
- **Anti-Proliferative – Inhibits cancer cell growth.**
- **Antioxidant – Prevents the damage of oxidation to other molecules in the body.**
- **Antispasmodic – Suppresses muscle spasms.**
- **Anxiolytic – While not fully recognized as an anxiolitic compound THC does seem to assist in the anxiety associated with PTSD.**
- **Appetite Stimulant – Δ9-THC is the only cannabinoid identified that is an appetite stimulant, giving people the stereotypical “munchies” many users describe.**
- **Euphoriant – Produces feelings of euphoria, promotes happiness and relaxation.**
- **Neuroprotective**

THC Metabolism

- 11-Hydroxy-Δ9-tetrahydrocannabinol (11-OH-THC) is the main active metabolite of THC.
- The conversion from THC to 11-OH-THC is relatively high when cannabis is consumed orally due to liver metabolism.
- 11-OH-THC crosses the blood–brain barrier more easily. This might partially explain the biphasic effects of cannabis, whereby some effects such as increased appetite tend to be delayed rather than occurring immediately when the drug is consumed.

THC Metabolism

- After administration through eating or drinking, approximately equal quantities of THC and 11-OH-THC are formed, whereas 11-OH-THC is a minor constituent after administration by intravenous or smoking routes.
- 11-OH-THC is subsequently metabolised further to 11-nor-9-carboxy-THC, which is not psychoactive but might still play a role in the analgesic and anti-inflammatory effects of cannabis.
- Metabolism occurs mainly in the liver by cytochrome P450 enzymes CYP2C9, CYP2C19, and CYP3A4.
- More than 55% of THC is excreted in the feces and ~20% in the urine

THC dosing – titration to effect

- Inhaled (vapourised) THC has immediate effects that the patient can titrate, with maximal effects at 4 minutes, and terminal effects ended by 4 hours.
- 1-2mg THC inhaled is a good starting dose but relatively impractical in the real world depending on the strength of the cannabis or THC resin.
- 0.1g cannabis or a less than a quarter of a SMALL would be a relatively equivalent visible amount

THC dosing – titration to effect

THC dosing – titration to effect

- Oral use is slower to titrate; start with 2.5-5mg THC, a dose factor of 2.5 increase over inhalation.
- Oral effects are variable from 30mins to 60mins, and lasting 4 to 8 hours generally, in a dose dependant manner.
- First dosing should be in a safe familiar location in case of adverse emotional feelings.

THC adverse effects

- Dose dependant*
- Red conjunctiva
- Increased hunger
- Euphoria
- Impaired short term memory
- Sedation and impaired cognitive function
- Anxiety, paranoia, thought disorder

THC adverse effects

- **High dose intoxication can lead to**
  - Extreme sleepiness/sedation
  - Cognitive deficits
  - Depersonalisation
  - Hallucinations/illusion
  - Acute psychotic reaction generally lasting hours but occasionally as long as a week. Radhakrishnan et al. Gone to pot – A review of the association between cannabis and psychosis. Frontiers in Psychiatry, 2014. 5 (54). doi: 10.3389/fpsyt.2014.00054

THC adverse effects

- **THC is associated with earlier presentation of symptoms of schizophrenia in those at risk**
- **THC is NOT associated with an increased rate of schizophrenia.**
- **Parker L. Cannabinoids and the Brain. Cambridge, MA; The MIT Press (2017).**
- **Hall W, Degenhardt L. "Cannabis use and psychosis: A review of clinical and epidemiological evidence". The Australian and New Zealand Journal of Psychiatry, 2000. 34 (1): 26–34.**
- **THC prescription is contraindicated in those with a personal Hx or Fhx of schizophrenia, or those at risk > screening tools:**
  - **Prodromal Questionnaire (PQ-16)**
    - Comparative CAARMS diagnosis with high sensitivity 87% and specificity 87%. Concurrent prodromal or psychotic SIPS diagnosis with 90% sensitivity and 49% specificity. Ising et al. The validity of the 16-item version of the Prodromal Questionnaire (PQ-16) to screen for ultra high risk of developing psychosis in the general help-seeking population. Schizophrenia Bulletin, 2012; 38(6): 1288-1296.

Cannabichromene - CBC

- Does not get you “high”; Not Psychoactive.
- Little is known about CBC’s exact pharmacokinetics, but binding to CB1 and CB2 appears very weak.
- CBC is a less potent analgesic and anti-inflammatory effects compared to THC and CBD.
- CBC is antibacterial and its acid precursor CBCa has been shown to be an antifungal agent.
- CBC is a bone stimulant and anti-neoplastic.
- CBC has also been shown to be ten times as powerful as CBD at reducing anxiety and stress.
- Decarboxylation by UV light, CBC becomes CBL, a cannabinoid we known relatively nothing about.

Cannabichromene - CBC

- **Pain reliever in rat studies via multiple MOA.** Maione S et l. Br J Pharmacol, Feb 2011; Vol 162(3): 584-96.
- **Anti-inflammatory effects.** Delong GT et al. Drug Alcohol Depend, Nov 2010; Vol 112(1-2): 126-33.
- **Antidepressant-like effect in stressed mouse studies.** El-Alfy AT et al. Pharm BioChem and Behaviour, June 2010; Vol 95(4): 434-442.
- **Positive effects on mouse adult neural stem/progenitor cells.** Shinjyo N, Di Marzo V. Neurochem Int, Nov 2013; Vol 63(5): 432-437.

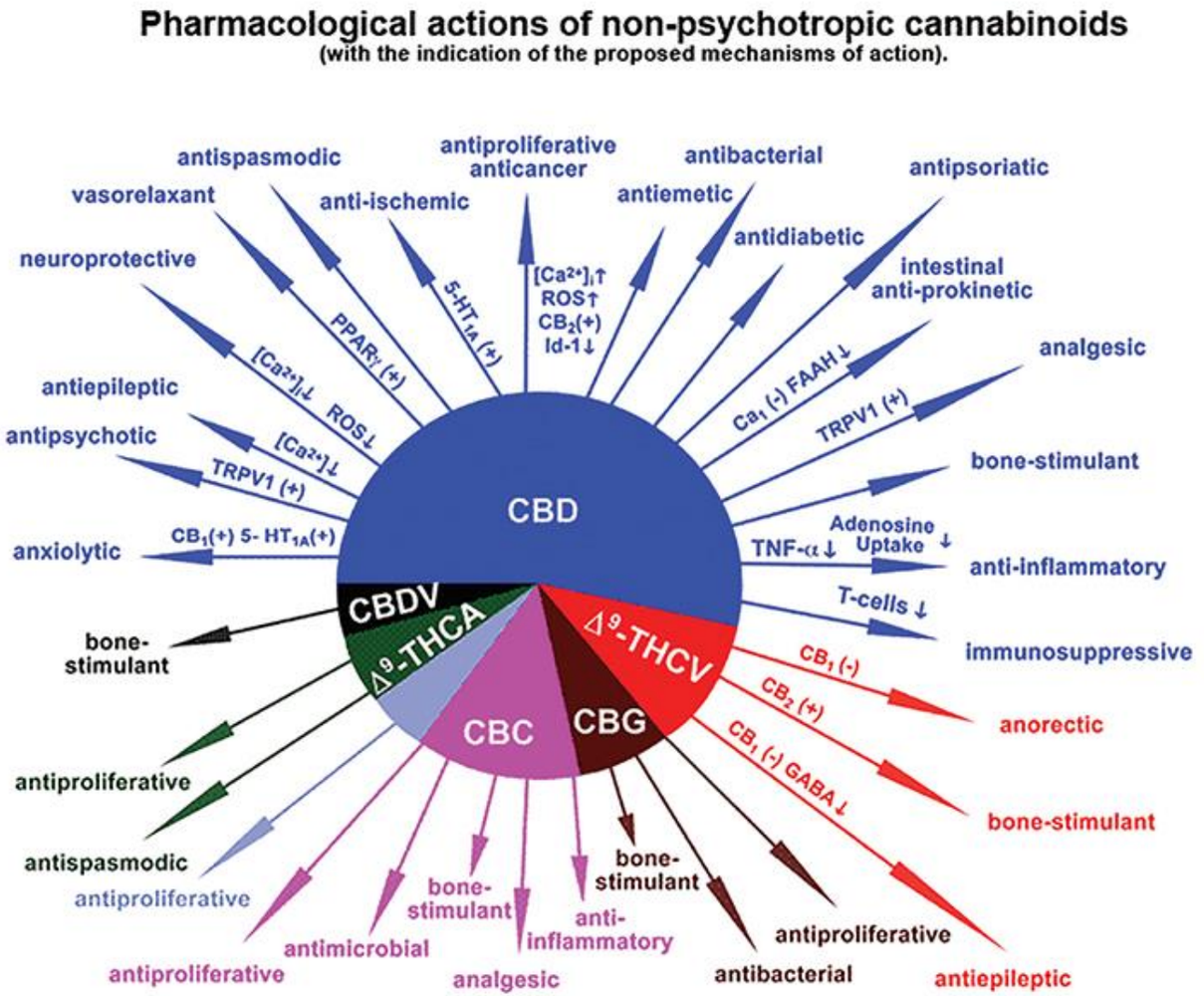
Cannabinol - CBN

- CBN is the breakdown product of THC.
- Mildly psychoactive.
- CB1 and CB2 agonist.
- Strongest cannabinoid to promote sleep.
- Highest in Indica strains.
- LD50 (Lethal Dose): 13500mg/kg for mice (Compare to Nicotine: for rats – 50 mg/kg, for humans – 0.5-1 mg/kg).

Cannabinol - CBN

- Formed as a metabolite of THC, ie if cannabis is exposed to air or UV light.
- CB1 partial agonist, but has a higher affinity to CB2; however with lower affinities in comparison to THC.
- Weaker psychoactive properties than THC.
- CBN has been shown to have analgesic properties.

Actions of non-psychoactive Cannabinoids



Cannabis “Juicers” - Raw Acid Cannabinoids

- **Dr. Courtney has researched the benefits of raw cannabis and has come to the following conclusions:**
  - Smoking cannabis may not treat the disease, only the symptoms
  - Therapeutic levels of cannabinoids are better achieved through ingestion
  - When cannabis is heated or burned, the chemical structure of the plant compounds are changed, specifically the acidity of THC, which alters its ability to be therapeutic
  - Raw cannabis activates the brain’s cannabinoid system, which triggers an antioxidant release
  - These antioxidants act as a “cleaner” and remove damaged cells from the body
  - Raw cannabis improves the efficiency of the cells in our body
  - Creating oils, butters or eating the raw plant is the best way to get the necessary beneficial compounds

Cannabis “Juicers”

- Juicing specifically takes a lot of material; Dr. Courtney suggests 20-30 big shade leaves or 2-3 raw buds (2-3 inches in length) per day for therapeutic benefits.
- Added to salads or sprinkled on foods.
- Keep below 100*c to remain non-psychoactive.

Cannabis Controversies

- **Recreational use**
- **IQ increase vs decrease**
- **Driving, exclusion period**
- **Non-seminoma testicular cancer risk***
- **Cannabis advancing onset of schizophrenia in those at risk of getting schizophrenia**
  - ?Due to high THC breeds. Evidence CBD is protective.
  - No evidence of causal effect

Chronic Heavy Smoked Cannabis

- Although airway cancer risk appears equivocal, no recommended
- Increased bronchial secretion, some COPD
- Evidence of decrease IQ
- Mitigate risks by vapourising or oral administration*

Cannabis Contraindications

- Unstable or severe cardiovascular disease
- Hypotension as Cannabis will lower blood pressure
- Psychotic illness or a risk of psychotic illness – remember to screen with PQ-16 Screening Test (Prodromal Questionaire)
- Addiction risk factors
- History of Cannabis abuse

Current Top Uses For Cannabis

- Pain
- Anxiety
- Depression
- Insomnia
- Spasm/Dyskinesia
- PTSD
- Nausea
- Epilepsy
- Neuroprotection

Cannabis Products

- Raw Cannabis
- Oil mixture, usually olive
- Juices
- Oral Tincture
- Hashish (pressed cannabis)
- Kief (dry sift)
- Resin
- Shatter
- Edibles / Drinks
- Dermatologicals

Cannabis Administration

- Vapourisation
- Smoke / Water Bong
- Dab / Spot
- Oral
- Rectal
- Dermal
- Buccal / Nasal

Cannabis Prescription

- **Patient screening, education and consent**
- **THC:CBD ratio product selection**
- **Government application**
- **Rx: THC 1-2mg dose vape/2.5-5mg oral**
  - Titrate gradually to effect
  - CBD alone products can start immediate high dose
- **Monitor, Review, Report**

Cannabis Products

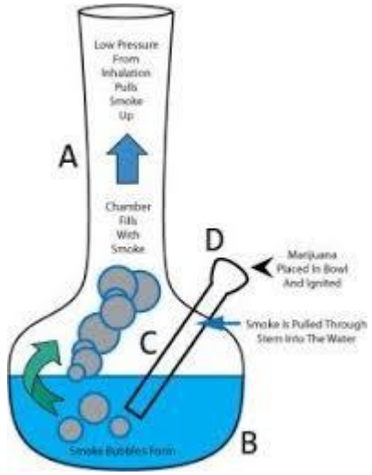
Cannabis Products

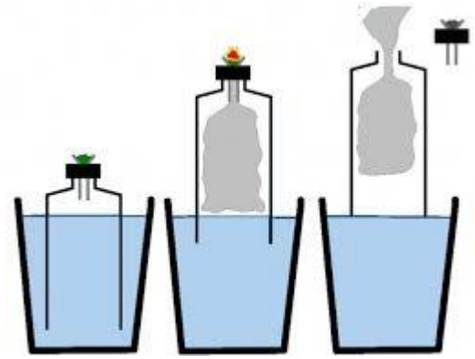
Cannabis CO2 Extraction

Cannabis Devices

Cannabis Devices

Cannabis Devices





Cannabis Devices

Cannabis Devices

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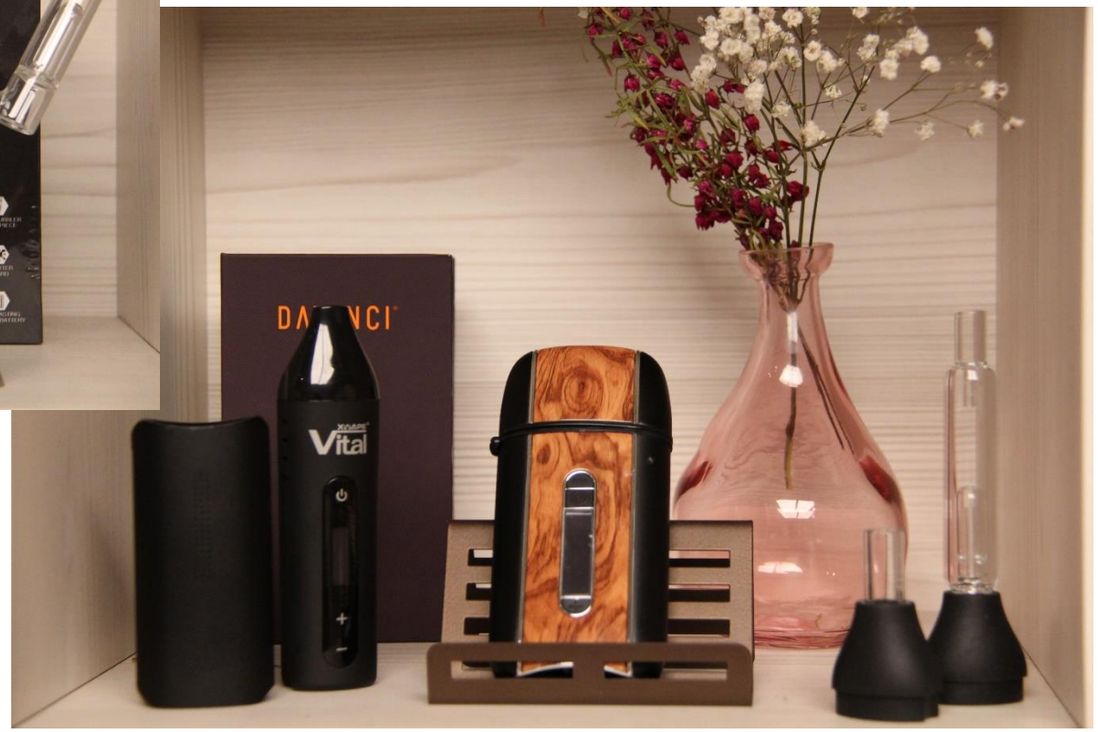
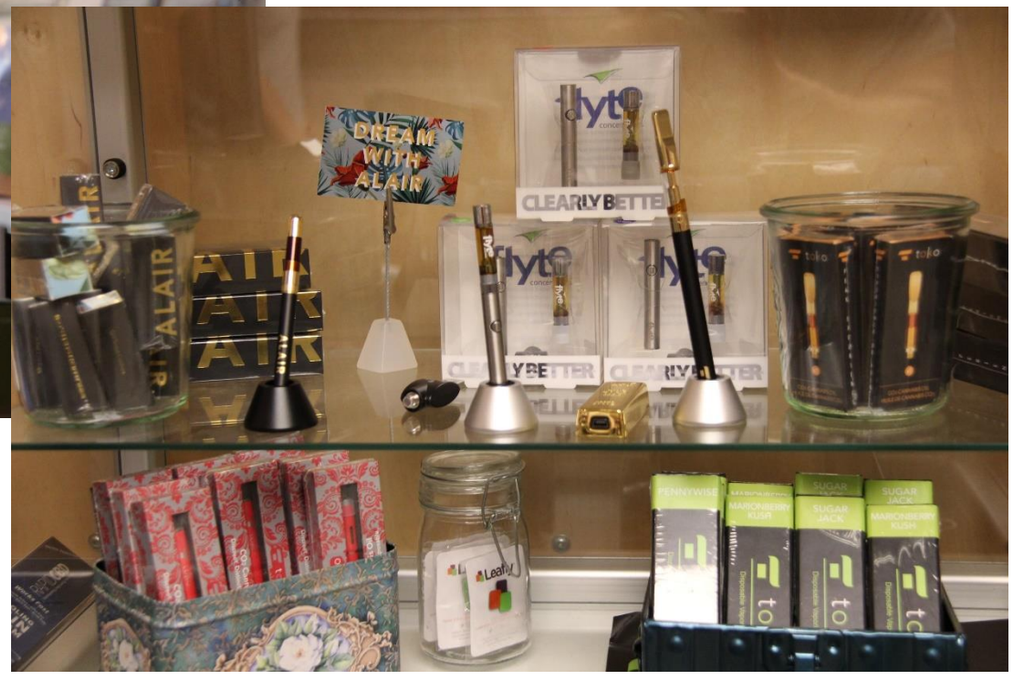
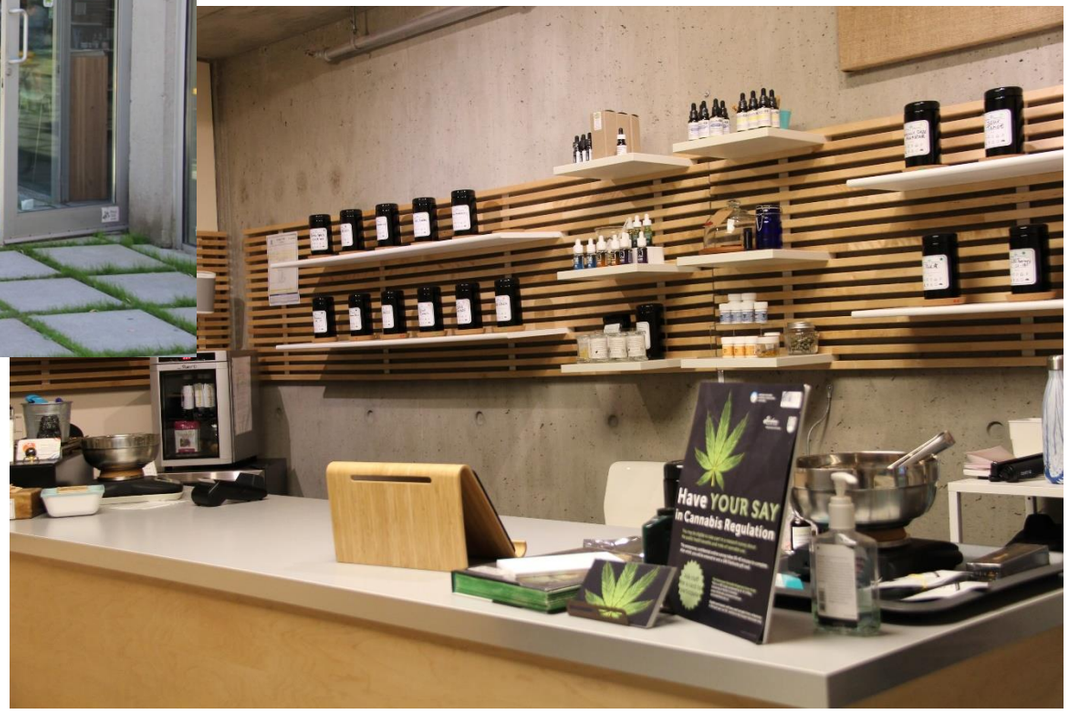


Cannabis Devices



Cannabis Dispensary



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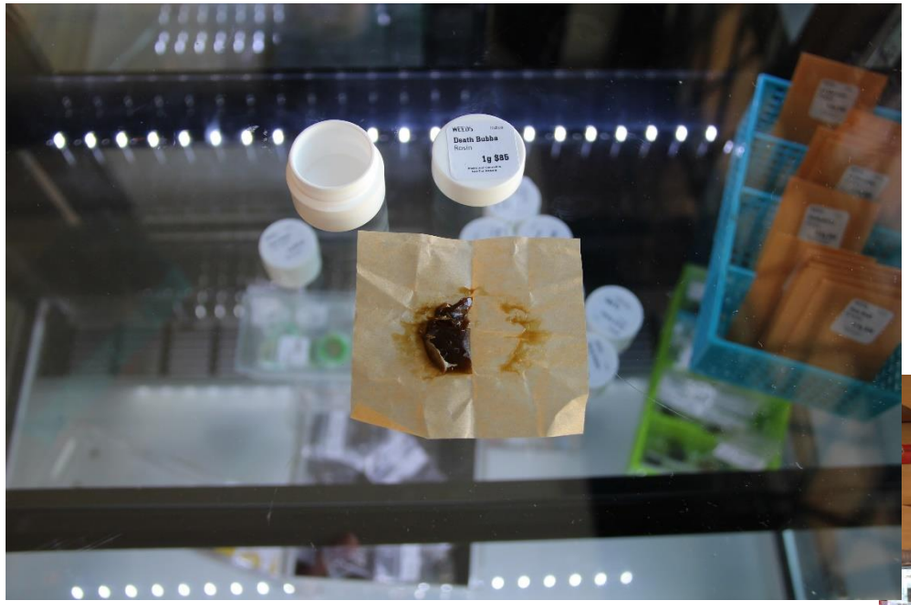

Cannabis Grow Facility Canada

Cannabis Prescription

- **Patient screening, education and consent**
- **THC:CBD ratio product selection**
- **Government application**
- **Rx: THC 1-2mg dose vape/2.5-5mg oral**
  - Titrate gradually to effect
  - CBD alone products can start immediate high dose
- **Monitor, Review, Report**

Take Home Messages

- Medicinal Cannabis does not need to get the patient “high” / neuropsychologically altered
- Start low and titrate dose to effect: THC 1mg
- No direct mortality from cannabis use
- CBD, among other cannabinoids, modulate THC effects
- The non-psychoactive natural raw acid forms of the cannabinoids are being used for CB2 reception modulation and preventing oxidative stress (among other effects)


Enjoy
Weed