

# CBD EXPLAINED

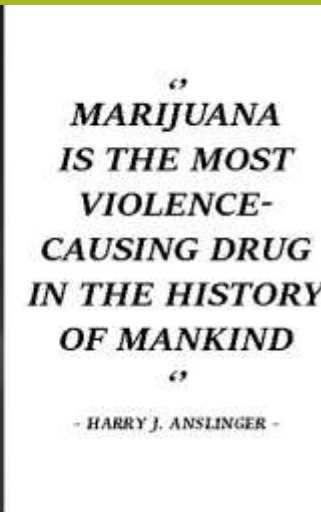
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Training with Professor Mike Barnes



# History

- Cannabis is the oldest medicine known to man
- It was used 5000 years ago in China as a pain medicine and for epilepsy
- Over the next centuries use as medicine spread slowly westwards and was used in ancient Egypt, Greece and Rome and in ancient Jewish and Arabic cultures
- It was totally accepted as a medicine up to the 1920's
- Pain was clearly an indication, including topical applications
- **Harry Anslinger:** First commissioner of the Federal Bureau of Narcotics- Began campaign against 'marijuana'



# Legal history

## PRIOR TO JAN 2019

- Cannabis was placed in the same category as morphine, heroin, and cocaine (UN Single Convention 1961)
- Schedule IV – “particularly liable to abuse and to produce ill effects, and such liability is not offset by substantial therapeutic advantages”
- Nearly all countries are signatories
- In UK led to Misuse of Drugs Act 1971
- Excluded industrial hemp

## RECENT REGULATORY CHANGES

- **Jan 2019:** European Food Safety Authority classifies Cannabidiol (Chemical component found in cannabis) as a Novel food synthetic or hemp derived
- **Nov 2020:** the EU highest court rules that CBD is not a narcotic
- **Dec 2020:** UN de-schedules Cannabis, it is no longer a narcotic



# THE CANNABIS PLANT

Often divided into 3 commonly cited strains:

- Sativa
- Indica
- Ruderalis

*"sativa/indica distinction as commonly applied in the lay literature is total nonsense and an exercise in futility"*

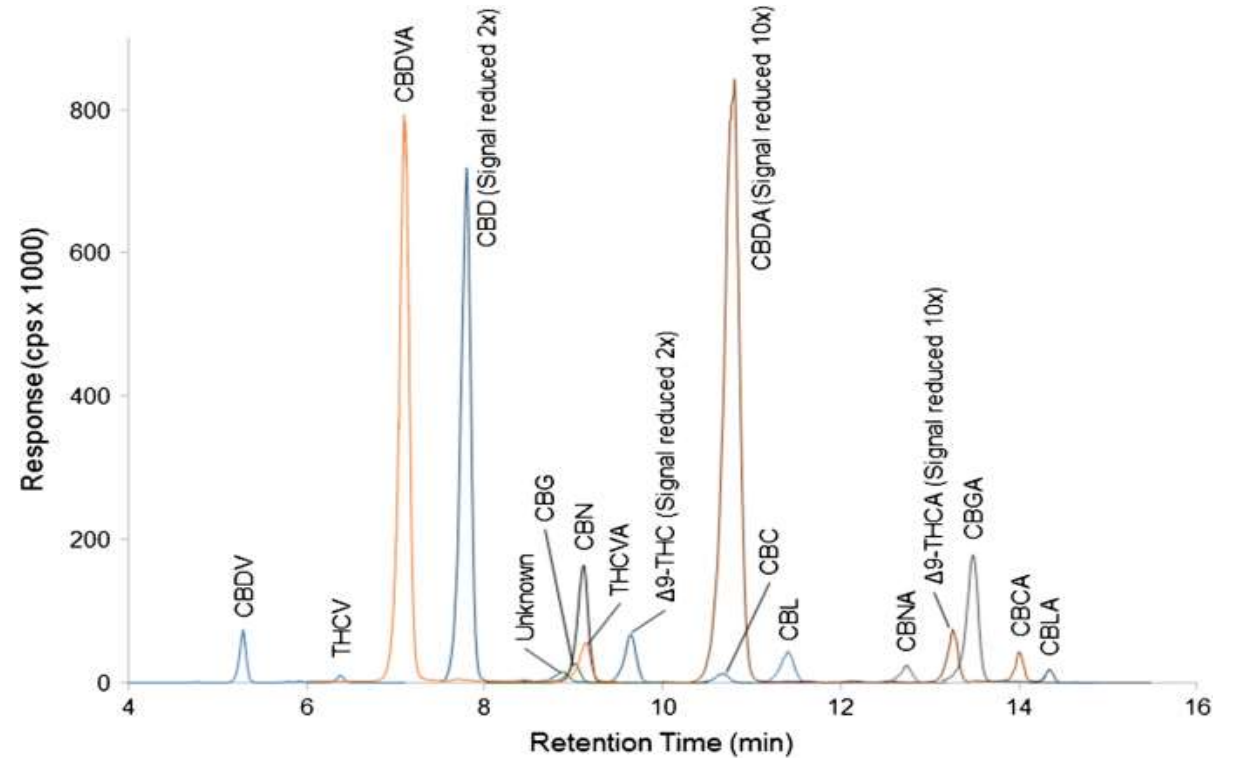
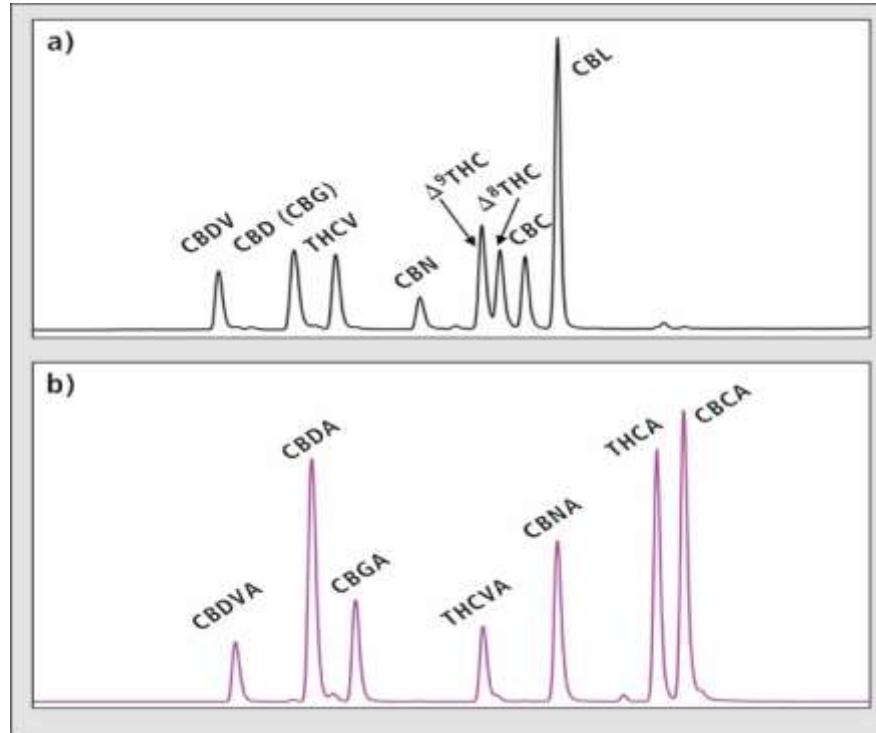
Ethan Russo

In reality; we now have over 2,500 different strains (cultivars) of the cannabis plant

The cannabis plant contains phytochemicals known as 'cannabinoids'  
each strain will have a different profile of these chemicals.....



... and therefore, unique biological activity

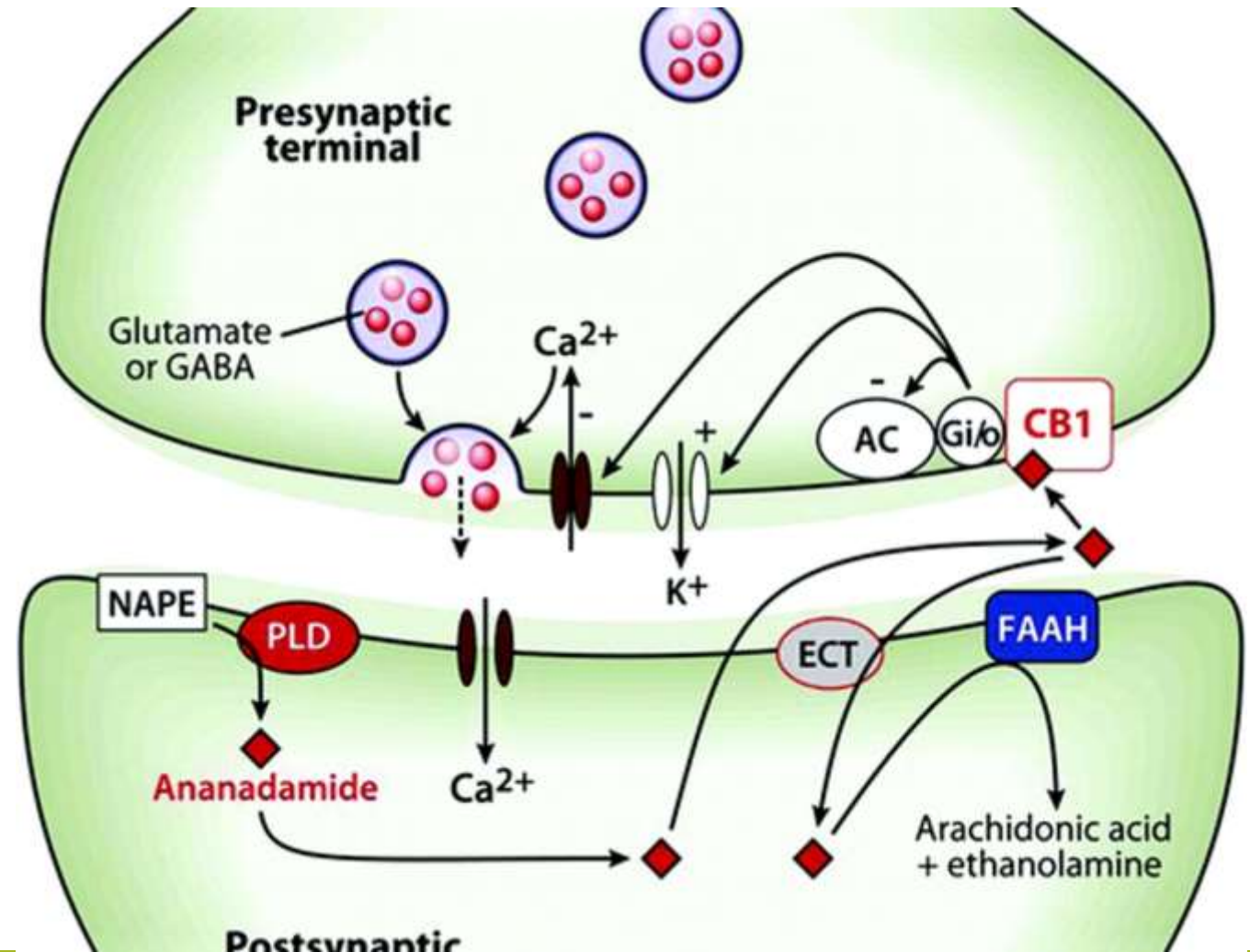


# What are Cannabinoids?

- A structurally diverse family of compounds that have many biological targets
- Over 100 cannabinoids have been identified
- Based on their origins, cannabinoids can be classified into 3 groups:
  - **Phtyocannabinoids**: Present in the whole plant (Stalks, leaves, flowers and seeds) over 100 identified
  - **Endocannabinoids**: Produced in the body and serve as intercellular lipid messengers
  - **Synthetic Cannabinoids**: Synthetically derived Cannabinoids that bind to the same receptors as Phtyocannabinoids

# We all produce cannabis – The Endocannabinoid System

- CB1 and CB2 receptors in every nerve ending in the body
- CB1 – CNS plus immune system, reproductive and GI systems as well heart, lung and bladder hypothesized to be receptor responsible for the intoxicating effects of cannabinoids
- CB2 – mainly immune system: likely roles of these receptors including modulation of cytokine release and of immune cell migration.
- Key chemical ligands that link to those receptors are **Anandamide** and **2-Arachidonoylglycerol (2-AG)**





# What does the endocannabinoid system do

## A widespread physiologic system, that displays many functions within the body:

- Regulates anxiety behaviour
- Memory – maybe a role in extinction of old memories and short term memory impairment
- Appetite – increased – mainly through CB<sub>1</sub> receptors
- Anti-inflammatory role
- Analgesia – probably also through PPAR alpha, TRPV<sub>1</sub> and GPR 55
- Sleep - promotes sleep and increases REM sleep
- Motor control – spasticity
- Neurogenesis and neuroplasticity
- Bladder (reduces tone)
- GI tract (reduces motility and anti inflammatory)
- Female reproduction – timing of embryonic implantation
- Control of some proliferative cell responses (anti-cancer)





# Natural Plant: Not that simple

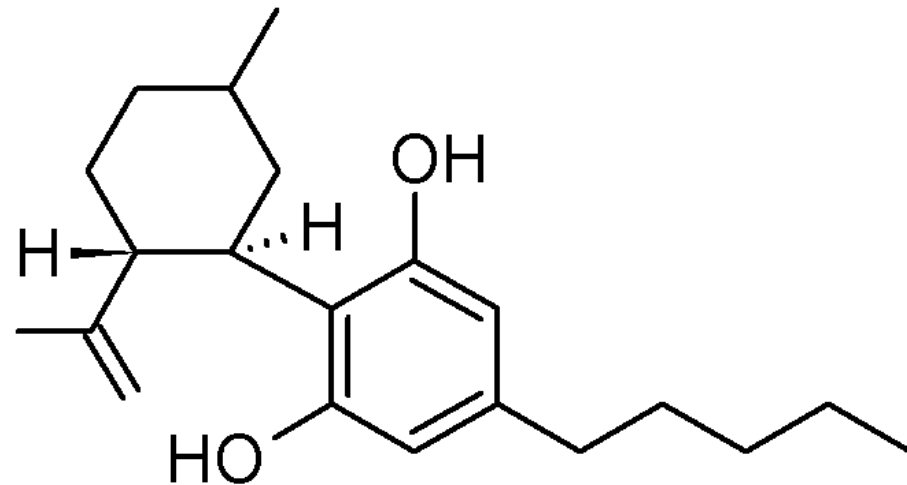
Over 100  
Phytocannabinoids  
identified

# A sample of some Cannabinoids

Cannabinoid	What we know	Cannabinoid	What we know
<b>Cannabigerolic acid (CBGA)</b>	<p>Considered the <b>mother of all cannabinoids</b></p> <p>Within the plant enzymes convert CBGA into some varying combination of precursor compounds:</p> <ul style="list-style-type: none"> <li>• THCA synthase converts CBGA to (Tetrahydrocannabinolic acid)</li> <li>• CBCA synthase converts CBGA to CBCA (Cannabichromenic acid)</li> <li>• CBDA synthase (CBDAS) forms CBDA (Cannabidiolic acid)</li> </ul>	<b>Cannabidivarinic Acid (CBDVA)</b>	<ul style="list-style-type: none"> <li>• Precursor to CBDV</li> <li>• <b>Non psychoactive</b></li> </ul>
<b>Cannabigerol (CBG)</b>	<ul style="list-style-type: none"> <li>• Cannabigerol (CBG) comes from Cannabigerolic acid (CBGA) after decarboxylation via heat or light: minor constituent</li> <li>• Non-psychoactive</li> </ul>	<b>Cannabinolic Acid (CBNA)</b>	<ul style="list-style-type: none"> <li>• Can be synthesised from THCA</li> <li>• Also a precursor of CBN, which is psychoactive</li> <li>• <b>Considered non-psychoactive</b></li> </ul>
<b>Cannabichromenic Acid (CBCA)</b>	<ul style="list-style-type: none"> <li>• Precursor to CBC, synthesised from CBGA by enzymatic action</li> <li>• considered a minor cannabinoid</li> <li>• <b>Non-psychoactive</b></li> </ul>	<b>Cannabinol (CBN)</b>	<ul style="list-style-type: none"> <li>• A degradation product of THC and is more broadly detected especially in older cannabis and cannabis extracts that have been exposed to oxygen or light over time.</li> <li>• <b>Weakly psychoactive</b></li> <li>• Believed to be 90% less psychoactive than THC</li> </ul>
<b>Cannabichromene (CBC)</b>	<ul style="list-style-type: none"> <li>• Research at early stage but is showing potential anti-inflammatory agent and analgesic</li> <li>• <b>Non psychoactive</b></li> </ul>	<b>Tetrahydrocannabinolic Acid (THCA)</b>	<ul style="list-style-type: none"> <li>• Precursor to THC</li> <li>• It is <b>not intoxicating itself however it metabolises to form THC</b> which is intoxicating</li> </ul>
<b>Cannabicyclol (CBL)</b>	<ul style="list-style-type: none"> <li>• Occurs in minor concentrations in plants</li> <li>• Degradation compound which comes from the degradation of CBC mainly due to exposure of UV light or Oxygen</li> <li>• <b>Non-psychoactive</b></li> </ul>	<b>Tetrahydrocannabivarinic acid (THCVA)</b>	<ul style="list-style-type: none"> <li>• Precursor to THCv</li> <li>• <b>Not thought to be psychoactive</b></li> <li>• Not thought to directly interact with CB1 and CB2 receptors</li> </ul>
<b>Cannabidiolic Acid (CBDA)</b>	<ul style="list-style-type: none"> <li>• Precursor to CBD; converts by thermal decarboxylation</li> <li>• <b>Non-psychoactive</b></li> </ul>	<b>Tetrahydrocannabivarin (THCV)</b>	<ul style="list-style-type: none"> <li>• Major Phytocannabinoid</li> <li>• Possesses almost identical structure to delta-9-THC however has different molecular targets</li> </ul>
<b>Cannabidiol (CBD)</b>	<ul style="list-style-type: none"> <li>• Major cannabinoid</li> <li>• Research suggests; effective for treating nausea, seizures, inflammation, insomnia, anxiety</li> <li>• <b>Non-psychoactive</b></li> </ul>	<b><math>\Delta</math>8- Tetrahydricannabidiol (<math>\Delta</math>8-THC)</b>	<ul style="list-style-type: none"> <li>• Isomer of delta-9-THC</li> <li>• <b>Psychoactive however considered less psychoactive than delta-9-THC</b></li> <li>• antiemetic, anxiolytic, appetite-stimulating, analgesic, and neuroprotective properties</li> </ul>
<b>CBE (Cannabielsoin)</b>	<ul style="list-style-type: none"> <li>• Metabolite of CBD</li> <li>• Not well studied; established in 1984 using CBD as a starting material</li> <li>• <b>Non-psychoactive</b></li> </ul>	<b><math>\Delta</math>9- Tetrahydricannabidiol (<math>\Delta</math>9 -THC)</b>	<ul style="list-style-type: none"> <li>• <b>Major Psychoactive cannabinoid</b></li> <li>• Synthesised from THCA and CBGA</li> <li>• Research has found THC to display a number of medically useful effects</li> </ul>

# Focus on CBD

- One of the major **Non-psychoactive** cannabinoids found in the cannabis plant
- According to the World Health Organisation CBD exhibits no effects indicative of any abuse or dependence potential; and is generally well tolerated with a good safety profile
- CBD interacts with the endocannabinoid system but also other neurotransmitter systems in the body such as the serotonin system and pain systems
- Has been demonstrated as an effective treatment of epilepsy in several clinical trials
- **What does it do?**
  - Neuroprotective
  - Anti-anxiety
  - Anti-convulsant
  - Cytotoxic in breast cancer (antagonises TNF alpha)
  - Anti emetic
  - Reduces the psychoactive effects of THC
- **Main uses:**
  - Anxiety (stress)
  - Aches and pains
  - Sleep
  - Skin care
  - (Epilepsy)



# Side effects



Mild and well  
tolerated



CBD has very  
few side effects



Main short-term  
problems –  
dizziness /  
drowsiness / dry  
mouth /  
stomach cramps  
/ diarrhoea

# Various methods of obtaining CBD

Ethanol extraction



Super Critical CO<sub>2</sub> Extractor



Synthetic derivation





# Synthetic CBD

- Synthetic CBD is **designed to mimic the DNA of CBD** found in Cannabis; it is chemically identical and binds to the same receptors in the body
- Usually derived from citrus starting source
- Two common derivatives of CBD have been identified: (-)- CBD and +(-) CBD.
  - (-)- CBD stimulates the CB2 receptor (primarily expressed on immune cells).
  - (+)- CBD has affinity for both receptors with the potential to display effects similar to THC ( psychoactive response)
- (-) - CBD enantiomer can be carefully synthesised to ensure no psychoactive response

# Variety of ways to take CBD



## Buccal / sublingual

Hold under tongue or buccal for 1-2 minutes

Fast absorption – minutes; Lasts 4/6 hours

Bioavailability depends on how long under the tongue / how much swallowed

Around 20% bioavailability



## Skin or buccal patch

Transdermal absorption



## Oral Spray

(Sativex)



## Oral

Variability of first pass metabolism

However there are new drug delivery systems being developed all the time such as films, nano delivery..

Food effects – better absorption after fatty meal

Metabolism – CYP variability (2c9, 3a4 and 2c19)

Effect 30-120 minutes, Lasts 4/8 hours

Excreted by urine (40%) and faeces (60%) but remains in fat stores for days (even a few weeks)



## Rectal or Vaginal

Avoids first pass metabolism



## Balm or salve

Applied directly to the skin  
Could be useful for inflammation