CANNABIS USE IN NEUROLOGICAL DISORDERS-

Parkinson's Disease
Amyotropic Lateral Sclerosis
Multiple Sclerosis
Crohn's Disease

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Objectives

- 3 neurological disorders that CB1 receptor from cannabis can down regulate through use of cannabinoids
- Understand how cannabinoid receptors modulate neuronal activity in human body



Definitions

- Hemp is Cannabis sativa L species grown commercially for seed & stalks
  - Hemp protein powder, food
  - Nutritional supplements
  - Textiles, building materials
  - Paper
  - Personal care products

  [Hemp contains no more than 0.3% THC dry weight]



Definitions

Hemp is higher in CBD (cannabidiol) than marijuana species Cannabis sativa L which is grown for THC psychoactive properties

Hemp oil- made from stalks, flowers, seeds

Hemp Seed Oil- cold pressed hemp seeds with trace amount CBD <25ppm (used as cooking oil

Hemp Essential Oil= no CBD, steam distilled flowers & leaves for soaps, cosmetics, perfumes, candles

Definitions

- CBD oil = thick, viscous oil from stalks & seeds (contains vitamins, minerals, fatty acids, terpenes, flavonoids)



Endocannabinoid System (ECS)

- Found in every mammal- regulates biological function through biochemical receptor- mediated regulation of intercellular calcium
- Cannabinoids are chemical compounds that bind to receptors throughout body=ECS
- Receptors in brain, lungs, liver, kidneys & immune system activated by therapeutic & psychoactive properties in cannabis

Edocannabinoid System

Martin Lee's description of ECS :

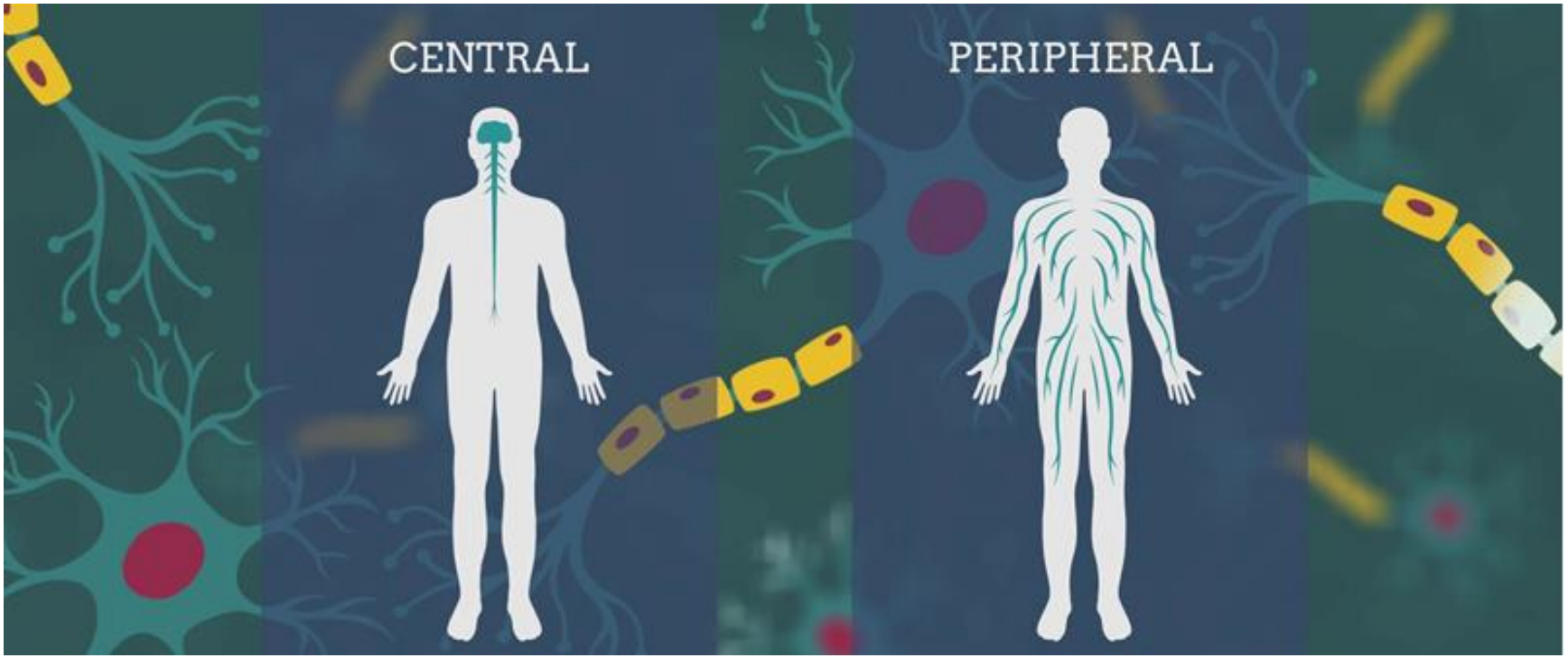
Immune system "kicks off like a furnace when a fever is required to fry a virus or bacterial invader. When the job is done, ECS turns down the flame, cools the fever and restores homeostasis".



Types of Cannabinoids

- Endocannabinoids- fatty acid cannabinoids produced naturally in body: anandamide (1992) & 2-AG (1995)
- Phytocannabinoids-oil resin of cannabis buds & leaves (THC, CBD) over 100 identified
- Synthetic- manufactured in lab to mimic effects of natural cannabinoids

Cannabinoid Receptors



CB1

- Modulates activity in brain & spinal cord (nausea, muscle spasticity, seizures)
- Function
  - Appetite regulation
  - Pain sensations
  - Execution of learned motor skills
- Dysfunction
  - Involuntary movements
  - Difficult starting/stopping movements-PD, Huntington's, Tourette-Syndrome

CB2

- Associated with immune system (splenocytes, macrophages, monocytes, microglia, B & T cells, glial cells)
- Function
  - Immune regulation
  - Managing inflammation
- Dysfunction
  - Immune disorders
  - Chronic inflammation
  - Astrocytes & microglia in PD = increased activity

TRPV1

- Transit receptor potential vanilloid-one
- Known for action with capsaicin
  - Mediates pain signals through different mechanism than endogenous cannabinoids & opioids (Russo 2013)

ECS Function

- Master homeostatis- mood, anxiety, appetite, reward, stress, pain
- ECS emerging target of pharmacotherapy since pain number 1patient complaint (Pacher, et al. 2006)
- Acute pain, persistent inflammation pain or neuropathic pain decreased through antinociceptive effects of cannabinoids
  - CB1 receptors open K+ channels & reduce response
  - CB2 receptors reduce signaling from immune cells

  (Sulak, Society of Cannabis Clinicians CME course)

ECS Function

Raphael Mechoulam's hypothesis:

"ECS serves human body analogous to the immune system. The immune system deals with invasive proteins while the ECS neutralizes non-protein insults like trauma or lack of oxygen

Normal ECS

- normal mental function
- no pain
- good digestion

Imbalanced ECS

- obesity or wasting syndrome
- metabolic syndrome
- diabetes
- liver fibrosis
- idiopathic bowel syndrome
- chronic pain
- neurodegenerative diseases

ECS Deficits

- Reduced ability to adapt to chronic stress-depletes ECS vigor (PTSD, neuropathic pain, depression, migraine, fibromyalgia, IBS
- Poor diet, environmental toxins, drug abuse, lack of physical activity, genetic factors

(Russo, et al, 2004, 2013)

ECS & Neurodegenerative Disorders

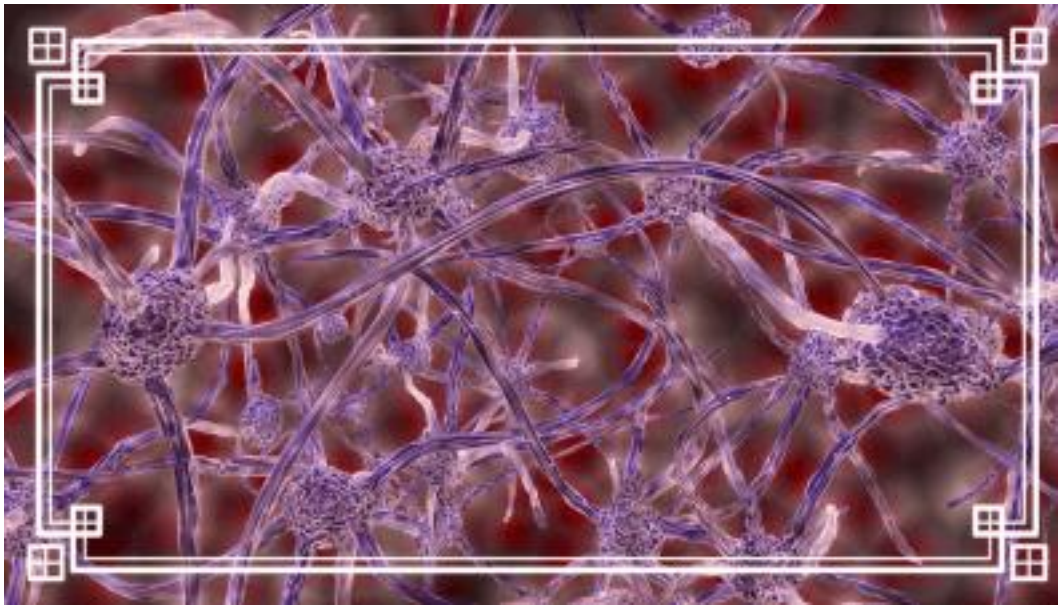
- Anandamide + 2-AG= endogenous neuroprotective
- Injury= excitatory neurons release glutamate which becomes toxic to surrounding cells ➔excitotoxicity
- Cannabinoids halt process (US Dept HHS patent on use of cannabinoids as antioxidants & neuroprotectants)
- Effect of cannabinoids has implications in treating MS, ALS, Alzheimer's, Parkinson's, Huntington's cholera

Multiple Sclerosis

- Autoimmune disease affecting central nervous system
- Myelin sheath damaged, exposing nerve cells which become inflammed & plaque formation disrupts electrical impulses moving between brain & rest of body= numbness, weakness, tingling, dizziness, fatigue, pain, difficult walking, slurred speech

Multiple Sclerosis

- Changes in ECS
  - CB1 receptor controls tremor & spasticity
  - CB2 receptor regulates inflammation



Parkinson's Disease

- Choreiform movements- rapid, jerky, involuntary movements associated with overactivity of globus pallidius/basal ganglia have been shown to respond to cannabinoid receptor activation (Lotan, et al, Clin Neurpharmacol 2014)
- Gowers textbook of neurology in 1888 recommended cannabis for PD!

Parkinson's Disease

- Long term use of L-dopa leads to depletion of SAMe needed for methylation + loss of GSH necessary for detoxification = more toxic damage (Kohlstadt 2009 Food and Nutrients in Disease Management)
- Restoring dopamine levels associated with flow of electricity to regulate fine motor control can result in Parkinson's tremor & other symptom resolution

Parkinson's Disease

- Tel Aviv University, Israel study 2017 reported medical cannabis improved PD symptoms in pilot study of 2 large movement disorder clinics- pain, sleep, mood- most patients smoked cannabis flowers & leaves (adverse effects reported as anxiety, confusion, hallucinations)
- Wang, et al 2013 J Clin Neuroscience reported 40% PD patients in US use CAM for disease management- reduce pain, improve sleep, relieve tremor, rigidity

Parkinson's Disease

- Cannabinoids = neuroprotective antioxidant/anti-inflammatory benefits with CBD/THC (Watzl, et al. Ad Ex Med & Bio 1991, Srivastava, et al. Immunopharm 1998, Mechoulam, et al. Chem & Biodiv 2007)
- Numerous studies indicate cannabinoids alleviate depressive symptoms (Hoogendijk, et al. Psychsomatic 1998, Yamamoto J Neurology 2001, Reijnders et al. Movement Disorders 2008)

Alzheimer's Disease

- Accounts for more than half cases of dementia affecting 30-50% over 85 (Benbadis, et al. Med Marj in Neuro 2014)
- Form of dementia with accumulation of amyloid-β & neurofibrillary tangles causing inflammation, oxidative stress, deficits in neurotransmission & cell death
- Cannabinoids= neuroprotective antioxidant effects (Hampson, et al Ann NY Acad Sci 2000), inhibit acetylcolinesterase (same as 3 FDA-approved drugs) + prevent A-β aggregation (Eubanks, et al. Mol Pharm 2006)

Alzheimer's Disease

- CB2 receptors stimulate decrease in microglial activation + lower amyloid-β levels in mice (Martin-Moreno, et al. J Neuroninflammation 2012)
- CBD shown to improve socialization + object recognition in transgenic AD mice (Cheng, et al. Psychopharm 2014)
- Dronabinol ↓ agitation, ↑ sleep + eating in dementia patients (Woodward Am J Geri Psych 2014)

Amyotropic Lateral Sclerosis

Most common degenerative disease of motor neuron system resulting in weakness of extremities (arms & legs) + breathing, swallowing, chewing.

Sx: pain, spasiticity, weight loss, dyspnea, depression

Compassionate care using cannabinoids to down regulate pro-inflammatory cytokines & chemokine production

Amyotropic Lateral Sclerosis

- Yiangou et al. BMC Neurol 2006 described spinal cord motor neuron damage- CB2 positive microglia/microphages signaling neuro-inflammation + oxidative cell damage
- Cannabinoids could delay onset + slow progression using THC and/or CBD
  - Shoemaker, et al J Neurochem 2007
  - Carter, et al. Am J Hosp Palliat Care 2010
  - Raman, et al. ALS other Mot Neuron Disord 2004

Amyotropic Lateral Sclerosis

- CBN (cannabinol) influenced disease progression + survival in mouse model (Weydt, et al. ALS other Mot Neuron Disord 2005)
- Non-psychotropic cannabinoids exert multiple pharmacological effects via CB1/CB2 receptors (Pertwee, et al. Pharmacol Rev 2010)
- Sativex (2.7mg THC + 2.5 mg CBD) in transgenic mice = effective in delaying ALS progression but decreased effectiveness during progression of disease

Crohn's Disease

- Life-long recurrent gut inflammation, pain + nutrient loss from medications
- Cannabinoids reduce gastric acid production, gastrointestinal motility, secretion transport
- CB1 receptors found in colonic epithelium & stomach parietal cells
- CB2 receptors found throughout gastrointestinal system- inflammation control, visceral pain, intestinal motility

Crohn's Disease

- Gertsch 2008 in Commun Integ Biol describes ECS + inflammation as "an ancient lipid signaling network which in mammals modulates neuronal functions and inflammatory processes" like those found in Crohn's disease
- Intestinal inflammation associated with up-regulation of intestinal CB1 receptors
- Isso, et al. Br J Pharmacol 2001 reported CB1 agonists inhibited intestinal motility in animal study

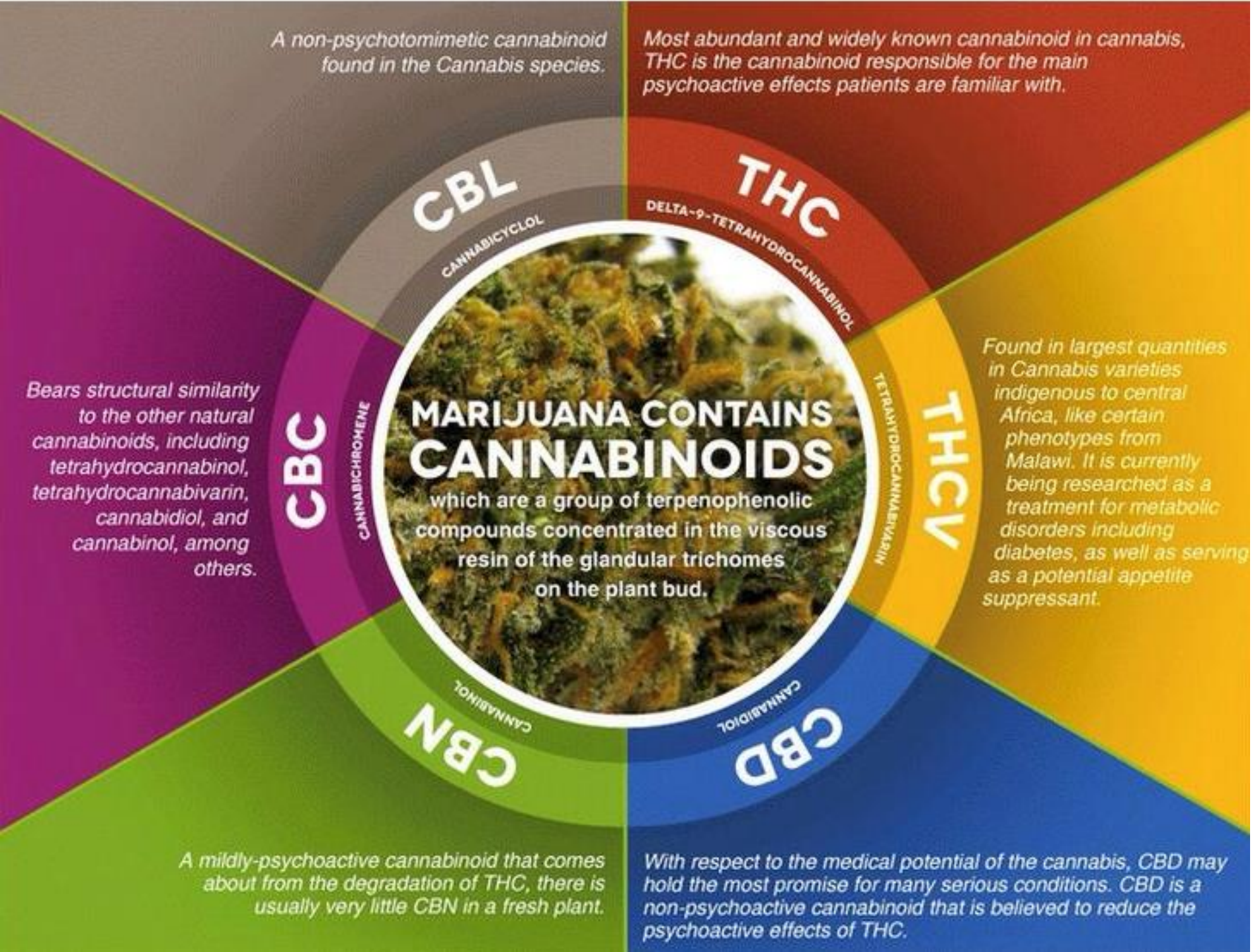
Crohn's Disease

- Natural protective role of ECS in Crohn's supported by
  - D'Argenio, et al. FASEB J 2006
  - Massa, et al. J Pharmacol Exp Ther 2004
  - Kunos & Pacher Nat Med 2004



Phyto-Cannabinoids

- Most effects due to THC influence on CNS
- High lipid solubility influences side effects in brain
- Low toxicity in phytocannabinoids
- Repeated use can produce abstinence syndrome if THC or CBD abruptly withdrawn
- “Cannabis Holiday”- several days to week= enhance effectiveness in THC


A non-psychotomimetic cannabinoid found in the Cannabis species.
CBL
CANNABICYCLOL
Most abundant and widely known cannabinoid in cannabis, THC is the cannabinoid responsible for the main psychoactive effects patients are familiar with.
THC
DELTA-9-TETRAHYDROCANNABINOL
Bears structural similarity to the other natural cannabinoids, including tetrahydrocannabinol, tetrahydrocannabivarin, cannabidiol, and cannabinol, among others.
CBC
CANNABICHROMENE
MARIJUANA CONTAINS CANNABINOIDS
which are a group of terpenophenolic compounds concentrated in the viscous resin of the glandular trichomes on the plant bud.
THCV
TETRAHYDROCANNABIVARIN
Found in largest quantities in Cannabis varieties indigenous to central Africa, like certain phenotypes from Malawi. It is currently being researched as a treatment for metabolic disorders including diabetes, as well as serving as a potential appetite suppressant.
CBN
CANNABINOL
CBD
CANNABIDIOL
A mildly-psychoactive cannabinoid that comes about from the degradation of THC, there is usually very little CBN in a fresh plant.
With respect to the medical potential of the cannabis, CBD may hold the most promise for many serious conditions. CBD is a non-psychoactive cannabinoid that is believed to reduce the psychoactive effects of THC.

Entourage Effect

Introduced 1998

- Shimon Ben-Shabat & Raphael Mechoulam
- All healing elements in plant + best results come from using whole plant

Cannabis= herbal plant
400 chemicals
>100 Cannabinoids



Raw Cannabis Plant

- Acid form- THCA, CBDA
- CBCA (cannabichromene) discovered 1966- non-psychoactive
  - Most abundant canabinoid produced (besides THC)
  - Interacts with other cannabinoids + TRPV1 and TRPA1 receptors
  - Found in cell membranes of animals where ion channel receptors interact with n-3 fatty acids
  - Considered “mother cannabinoid”= transforms into THCA, CBDA, CBCA, CBG (cannabigerol)



Hemp field
University of Kentucky

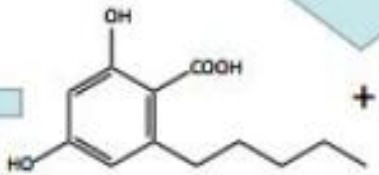


Cannabis flower GW Pharmaceuticals



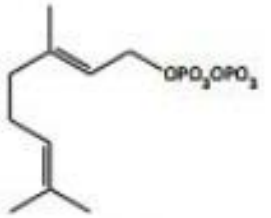
Capitate glandular Trichomes
GW Pharmaceuticals

Precursors



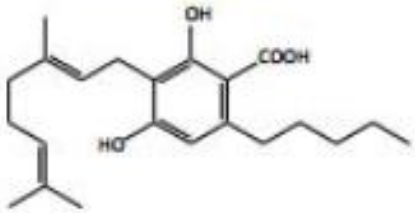
Olivetolic acid (5-pentyl resorcinolic acid)

+



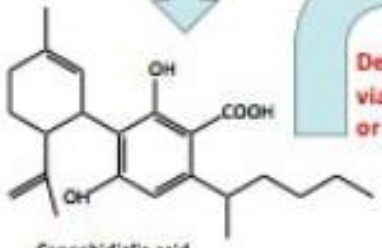
Geranyl pyrophosphate

Geranyl phosphate: olivetolate geranyltransferase



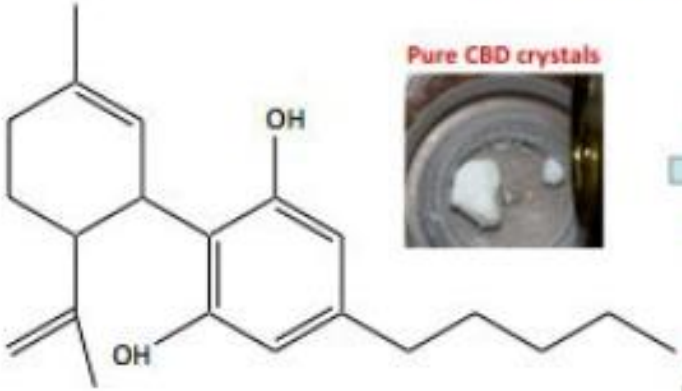
Cannabigerolic acid

CBDA synthase



Cannabidiolic acid

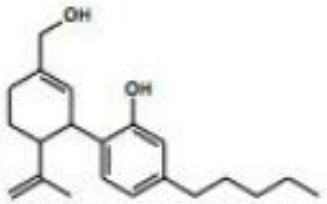
Decarboxylation via heat, light, or aging



Cannabidiol

Pure CBD crystals

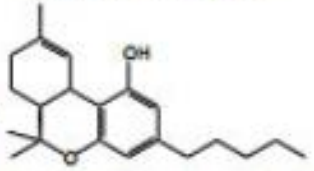
Hepatic metabolism



7-hydroxy-cannabidiol

Strong acid

(in vitro only)



Delta-9-tetrahydrocannabinolic acid synthase (THC)



Decarboxylation

- Heating & drying of cannabis activates cannabinoids for use in body
  - THC: psychoactive, euphoric, analgesic, bronchodilator, appetite stimulator, anti-convulsant, sleep-inducing
  - CBD: anti-inflammatory, anti-anxiety, anti-convulsant, neuroprotective, immune modulating

Terpenes

- Over 100 phytocannabinoids
- >200 terpenes work synergistically with cannabinoids
  - Lowers inflammation
  - Regulates blood glucose
  - Protects neurons & GI cells
  - Chemo-protective effects

  (Russo Br J Pharmacol 2011)

Terpenes

- Act as growth regulators, defense regulator, defense secretor & pollinator attractant (Hoffman Med Herbalism 2003)
- Cannabinoids + terpenes = improved effects of cannabis for modulating pain & inflammation (McPartland, Russo J Cannabis Ther 1)

Prescription Cannabinoids

- Dronabinol/Marinol= synthetic form of THC as sticky man-made resin formulated from sesame oil requiring liver metabolism with estimated 10-20% effectiveness/capsule
  - Treat anorexia in AIDS, nausea in chemotherapy
  - Available 2.5, 5, 10 mg capsules
  - Syndro= liquid formulation

Prescription Cannabinoids

- Nabilone/Cesamet= synthetic cannabinoid similar to natural substances
  - Activate CB1receptors to reduce nausea, vomiting
- Sativex (Nabiximole/Nabiximols)= oromucosal spray of cannabis sativa containing delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) in 1:1ratio used to treat pain, spasticity in MS


Is CBD oil addictive?

Is CBD Addictive?

- Addiction is chronic brain condition compelling continued use
- Addiction substances target brain's dopamine reward system
- Regular use of substances causing brain dopamine euphoria/happy response= continue use
- CBD is non-psychoactive, interacts with immune system
  - THC binds to CB1 receptors= intoxification
  - CBD serves as CB1 receptor antagonist to tone down THC effects (Indiana U study)

Ways To Use Cannabis in Neurological Diseases

- Smoking & Vaporizing
- Smoking is classic delivery- powdered flower/resin
  - Rapid onset 10 min
  - Cheapest delivery system
  - Lasts 2-4 hours (15% THC)
- Vaporizing heats cannabis to 180-200*C (356-392*F)
  - Better for respiratory tract
  - No terpenes [cannabis aroma]

Ways To Use Cannabis in Neurological Diseases

- Oral Edible Intake = delayed onset
  - Peak concentration 4-6 hours
  - THC converted to psychoactive + sedative
  - Bioavailability based on fat content of food, gut mobility, food preparation
  - Easy to overdose on THC edibles
- Capsules available 10-50 mg doses used 2-3 times/day
- Suppositories- rectal use for sedation + pain relief
- Raw leaves- salad, juiced 3-4 times/day
  - Medical benefits of cannabinoid acids

Dosing Guidelines

- Provide safe & effective recommendations
- Chemotherapy patient's needs different than Parkinson's patient
- LOW dose and SLOW increase
- Edibles more difficult to dose

Dosing Guidelines

- Decide format- nasal spray, oil, edible, vaping
- Ratio THC and/or CBD
- Space out dose over 8-10 hours (not single dose)
  - Inhalation 5-6 x day
  - Sublinguals 3-4 x day
  - Edibles 2-3 x day
- Repeat same dose 4-7 days before increasing
- Mayo Clinic recommendations for specific diseases on website
  - ALS: 10mg THC orally per day
  - MS: 2.5 mg dronabinol orally per day or 15-30 mg cannabis extract capsules orally in 5 mg doses or spray Sativex 8 x every 3 hours

Dosing Edibles

- Wide variety of infused edible products available in various potency levels: chocolates, lozenges, brownies, cookies, cupcakes, confections
- Colorado in 2014 reported 1.96 million units of edible medical cannabis-infused products and 2.85 million units sold in 2015 (~45% total cannabis sales in state) [Brohl, et al.CO Dept Rev 2015]
- Edibles avoid issues of odor & stigma of use + easier to transport



Serenity Hemp Extract Gummies 300mg - Full spectrum Hemp Gummy Bears - 10mg per gummy - 30ct - Tastes Like Hemp - Pain ...

by Serenity Hemp Company

$37.99 ($1.27/Count)

★★★☆☆ 141

✓prime

Get it by **TODAY, Feb 2**

FREE Shipping on eligible orders



35ct Premium Hemp Gummies - 15mg Per Gummy Bear - Organic Full Spectrum Hemp - Relief for Stress, Inflammation, Pain, Sleep,...

by Elite Hemp Products

$39.46 ($1.13/Count)

★★★★☆ 237

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Save $2.00 with coupon

Get it by **Tomorrow, Feb 3**

FREE Shipping on eligible orders



1/2 Baked Brownzzz Relaxation - 3 Pack

by Sippin' Syrup

$17.59

★★★½☆ 39

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FREE Shipping on eligible orders

Dosing Edibles

- Cannabinoids in edibles digested by liver enzymes (CYP 450) hydroxylates THC to 11-OH-THC which crosses blood-brain barrier (Grotenherman Chem & Biodiver 2007)
- Several studies indicate 11-OH-THC more potent than delta-9 THC
- State laws require total mg THC and number of servings per package
- CO equivalency: 1 mg THC in edible = 5.7 mg THC smoked cannabis
- CO & WA define serving as 10 mg THC

[Vandrey JAMA 2015]

CBD & Cannabis Infused Dark Chocolate

10mg CBD / 10mg THC
Pack of two 5mg CBD / 5mg THC Chocolates.
CBD

Cannabis Infused Mixed Fruit Chews

60mg THC
Pack of six 10mg THC fruit chews. Mix of Strawberry and Orange Cream.
Sativa

Cannabis Infused Coconut Oil

100mg THC
Each dropper contains 5mg THC, and c
Sativa



CBD as Dietary Supplement

- Begin small: 1.25 mg CBD oil sublingual daily 2-3 x daily
- Capsules: low dose 10-15 mg CBD daily; high dose 25-100 mg daily
  - Increase weekly to desired level symptom management (150-200 mg daily severe neurological disorders, 50-100 mg daily migraine, fibromyalgia)
- 1 teaspoon CBD oil (25-30 mg) as salad dressing or added to smoothie, guacamole, pesto on spaghetti

THC side effects

- Euphoria: 20-30 minutes post inhalation
- Drowsiness/sleepy: dose related
- Tachycardia or rapid heart rate: 10-20 min after inhalation + can last 60 min
- Increased appetite: soon after use
- Dry Mouth: follows THC use

Summary

- Every individual is unique- different speed of correcting inflammation
- Chronic diseases need large data sets to determine contributors & treatment options which are lacking in cannabis
- Single intervention for 1 symptom will not achieve results- diet, lifestyle + psychological beliefs about life underlie disease
  - What you eat
  - Quality of sleep
  - How you live your life
- Could underlying deficiency of naturally occurring endocannabinoids be leading cause of neurodegenerative disorders?
  - Neuroplastic ability of brain vs decline with age
  - Brain can heal & grow more connections if adequate stimulators & nutrients provided



CANNABIS

A Clinician's Guide



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CRC Press
Taylor & Francis Group