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Cannabis and Cannabinoids from an Ethnopharmacological Perspective

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- Endocannabinoid system

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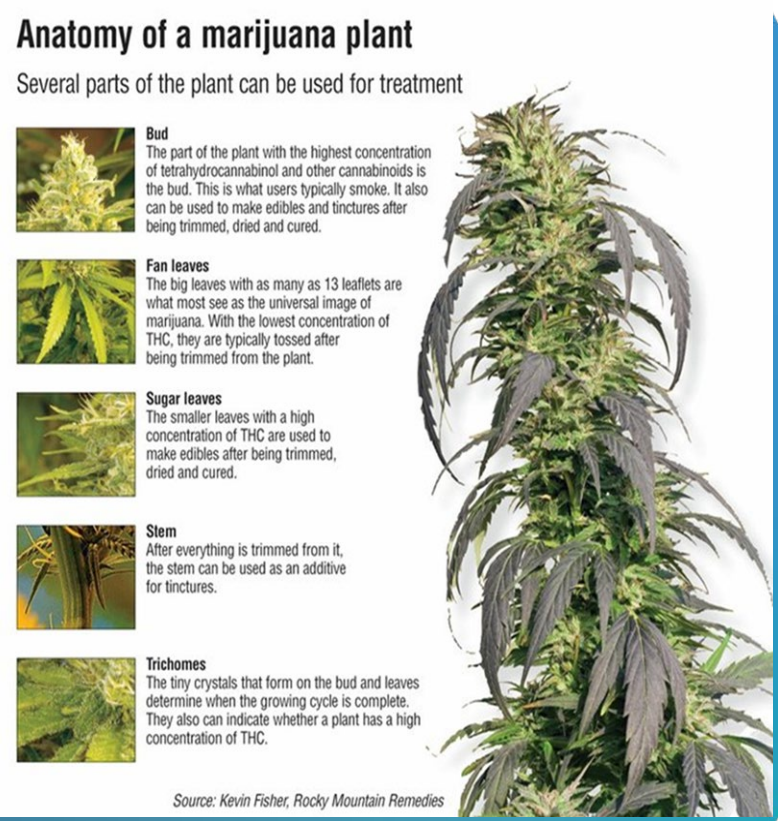
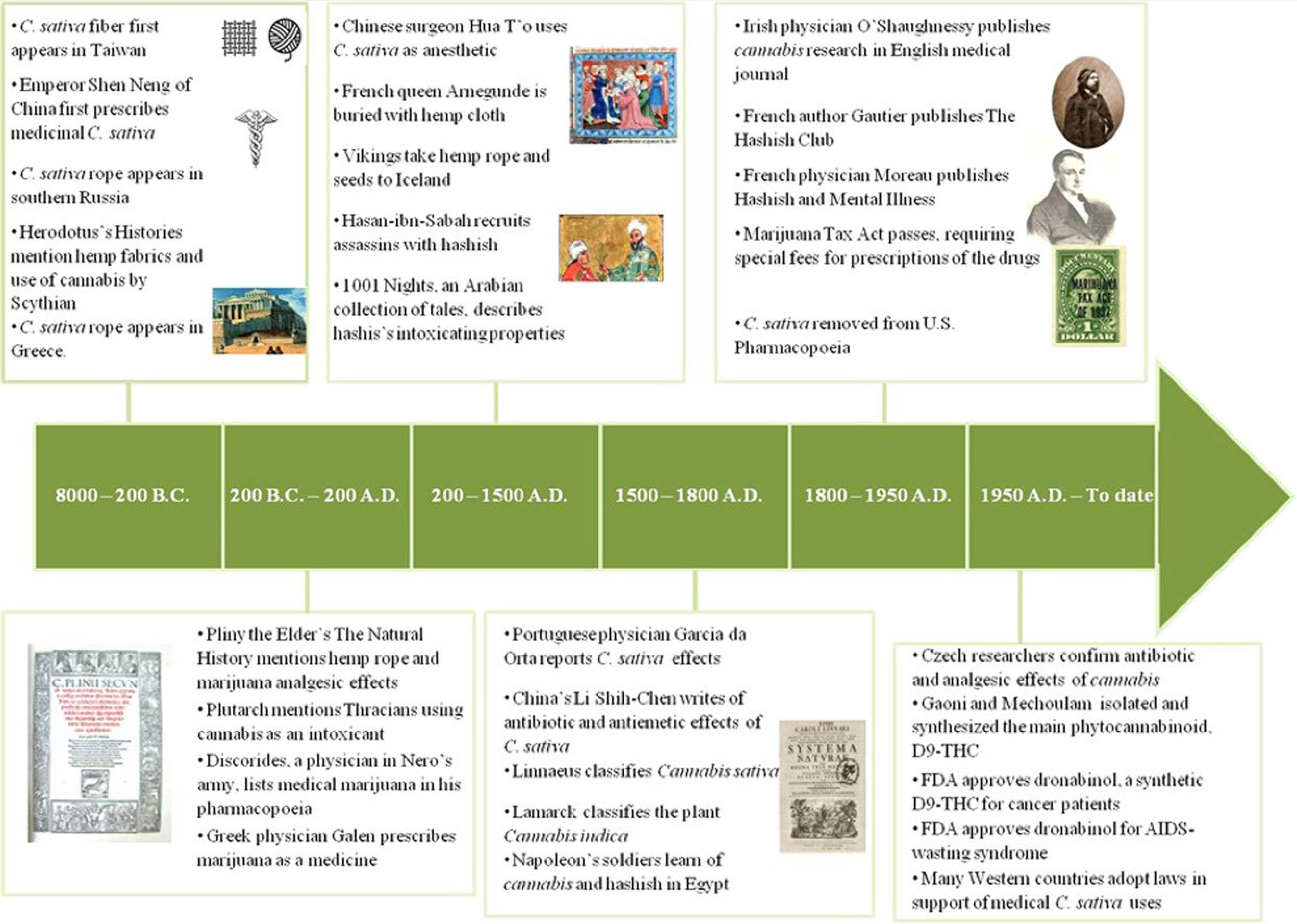


Cannabis sativa

- Annual dioecious plant
- Shares its origin with the first agricultural human societies in Asia over 8000 B.C.
- Over the course of time, different parts of the plant have been utilized for therapeutic and recreational purposes
- Oil was extracted from the hemp seeds while the inflorescences were heated for their psychoactive effects
- Currently there are hundreds of Cannabis cultivars and hybrids worldwide, each with unique and distinct chemical profiles
- Most studies focus on the trans-delta 9 – tetrahydrocannabinol (THC) and cannabidiol (CBD) however there are over 140 cannabinoids among the 400 compounds found in cannabis (milieu of terpenoids, flavonoids and other compounds with potential therapeutic activates)

(Procaccia S, et al. Frontiers 2022; Bonini SA, et al. J of Ethnopharmacology 2018)



(Bonini SA, et al. J of Ethnopharmacology 2018)

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Introduction

- The past 2 decades has seen a major increase in the use of medicinal Cannabis
- The therapeutic qualities are due to the naturally occurring family of secondary metabolites – Phytocannabinoids e.g. THC (first isolated in 1964 by Mechoulam), and CBD (first extracted in 1940 by Adams and elucidated in 1963 by Mechoulam)
- In 1980's CBD oil was gaining interest as it was found to possess anti-epileptic properties
- Over 140 distinctive phytocannabinoids have now been identified
- In addition, the isolation of phytocannabinoids from Cannabis, has led to the discovery of endogenous cannabinoids (endocannabinoids, eCBs) in 1992 by Devane.

(Procaccia S, et al. Frontiers 2022; Mechoulam R, et al. 1964; Adams et al. 1940; Mechoulam and Shvo, 1963, Devane et al. 1992; Hanus et al, 2106;

Pre and Post Harvest Conditions

- Concentrations of different compounds in the plant depend on many factors
- A strong genotype influence occurs on the composition of secondary metabolites in the different chemovars.
- Environmental factors can cause a very large variation in genetically identical plants when grown under different conditions
- Important factors include: humidity, light quality and intensity, CO_2 concentration and mineral nutrition.
- Most phytocannabinoids are synthesized in glandular trichomes located on the highest density of the inflorescences of unfertilized female plants (flowers, fan leaves, inflorescence leaves, stalk and stem).
- The composition and concentration of the different secondary metabolities are also affected by harvest time as well as storage conditions and duration.

(Aizpurua-Olaizola et al. 2016, Welling et al. 2018; McGarvey et al. 2020; De Backer et al. 2019, Berman et al. 2018, Chandra et al 2008; Chandra et al. 2017, Happyana and Kayser, 2016)

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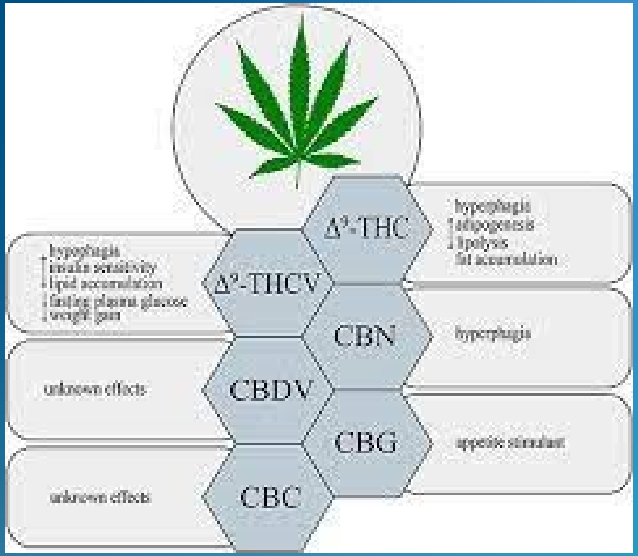
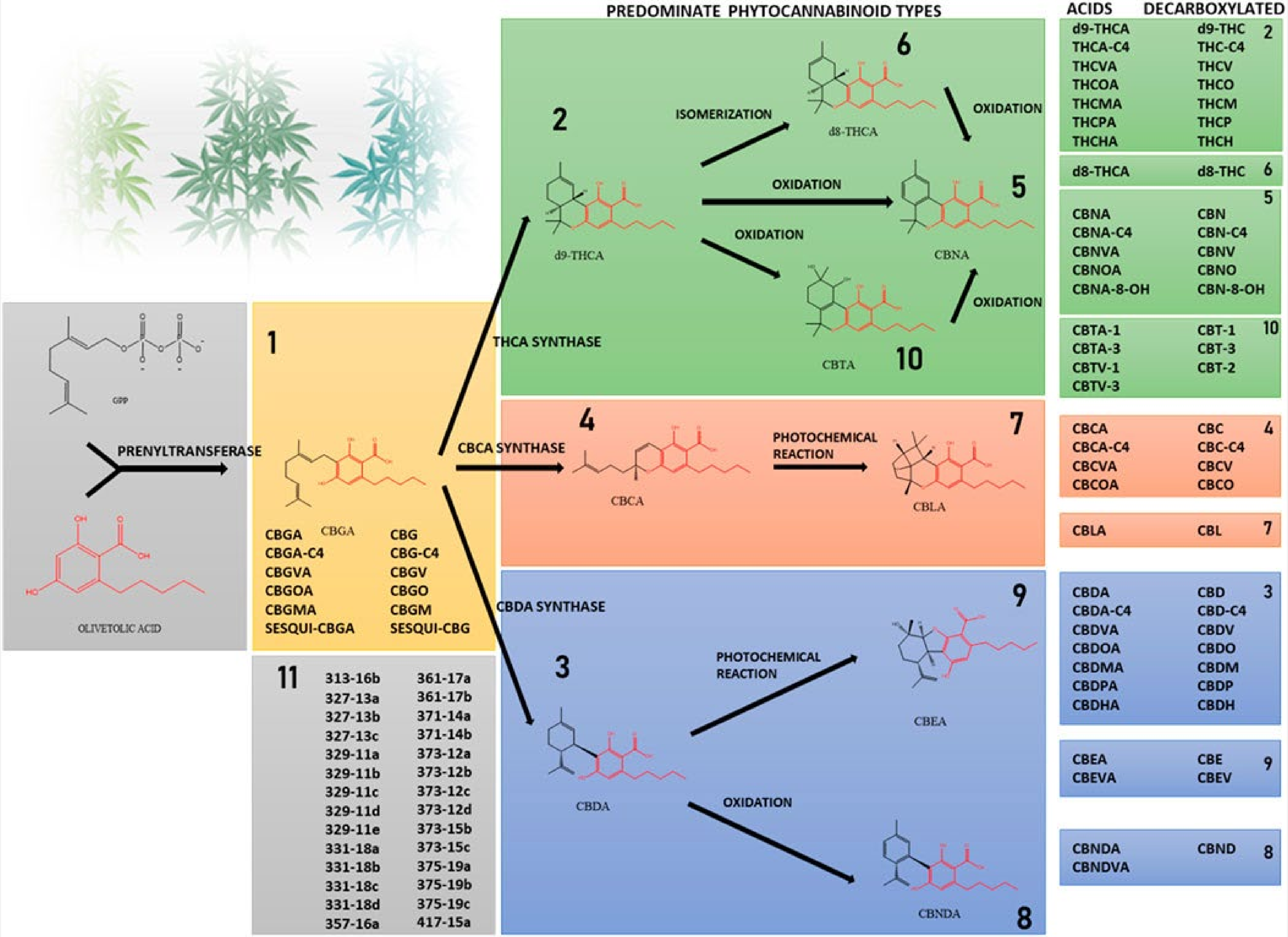
Phytocannabinoids



Bielawiec P et al. Frontierse Endocrinol. 2020

- Conventionally classified into 10 subclasses based on their chemical structure with an 11th miscellaneous type group
- All lipophilic compounds biosynthesized by the convergence of two main plant pathways: polyketide and plastidial non-mevalonate-dependent isoprenoid (MEP) pathway
- They have a resorcinyl core with a carboxyl group (COOH) on the aromatic ring, an alkyl side-chain of varying length that typically contains an odd number of carbon atoms (one to seven carbons), and a terpene moiety
- Only four subclasses are biosynthesized in the plant
- All remaining subclasses are the result of different degradation routes and chemical process such as oxidation, photochemical reactions, double bond isomerization etc

(Hanus et al, 2016; Berman et al, 2018; Gulkck and Moller, 2020.)



(Procaccia S, et al. 2022)

- Predominant psychotropic component is Δ9-tetrahydrocannabinol (Δ9-THC) is the most abundant form of THC
- Partial agonists or antagonists at the prototypical cannabinoid receptors, CB1 and CB2
- Higher permeability across the blood brain barrier
- Causes the intoxicating effect people feel e.g. altered perception of time and events, giddiness, increased focus, relaxation, anxiety, difficulty thinking and speaking, increased appetite, red eyes, slowed reaction time etc.
- THC releases large amounts of dopamine in the brain
- Delta-9 THC potential benefits: relaxation, sleep, reduced anxiety, increased appetite, heightened imagination, anti-inflammatory, reduction in pain, anti-cancer properties
- More interest is now being direct to delta-8 THC
- Both delta-8 THC and delta-9 THC can cause intoxicating effects but the plant naturally contains large amounts of delta-9 but very little delta-8
- Delta-8 THC potential benefits: pain relief, improved sleep, calming, improved appetite, sensory overstimulation prevention, and reduced inflammation.

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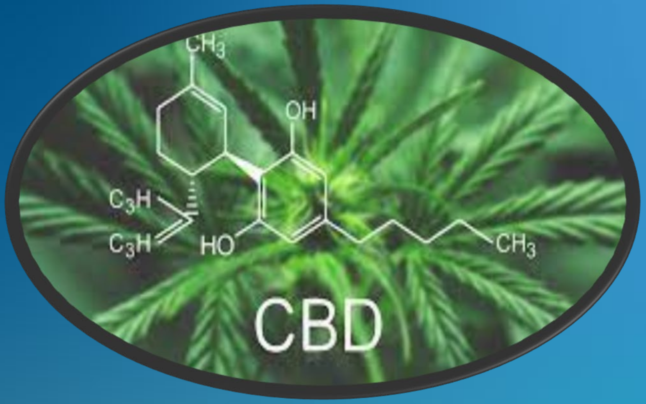
CBD



- Second most prevalent active ingredient in cannabis
- Does not cause the intoxicating effect like THC
- Touted for a wide variety of health issues and is considered to be safe
- Strongest evidence is for its anti-epileptic treatment particularly for Dravet syndrome and Lennox-Gastaut syndrome which typically do not respond to anti-epileptic medication
- It has also been found to reduce anxiety, help with insomnia, chronic pain relief and has been used to reduce addiction
- Scientifically it slows down messages being sent to the brain, changes calcium levels in the brain cells and reduces inflammation in the brain.

(Iffland K, Grotenhermen F. 2017)

CBN

- Products have claimed that cannabinol (CBN) has unique sleep-promoting effects
- The first phytocannabinoid to be identified in the Cannabis sativa L. plant by scientists in the 1930s.
- Unlike other phytocannabinoids, CBN is not biosynthesized in an acid form by the plant but is a degradative product of delta-9-THC.
- Concentrations in plant material and extracts are low due to this degradation, but increase over time as THC is exposed to light, oxygen, and heat
- Is a partial agonist of the CB1 receptor with a lesser affinity than THC
- This receptor is said to be responsible for the “psychoactive” effects of Cannabis spp., including sleep-related effects such as sedation

(Corroon J. Cannbinoid Res. 2021)

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THCV - Δ(9)-tetrahydrocannabivarin

- A naturally occurring analog of THC but is a non-psychoactive phytocannabinoid that has been found to affect lipid and glucose metabolism in animal models.
- Reported to behave as both a CB1/CB2 agonist and/or a CB1/CB2-neutral antagonist, most likely dose-dependent, with agonism observed at high doses and antagonism at low doses
- Other target sites of action include GPR55 and transient receptor potential channels
- THCV in rodents at 3, 10, and 30 mg/kg body weight caused hypophagia and weight loss, with food intake and body weight returning to normal on day 2
- Diet-induced obese mice, received oral THCV (2.5–12.5 mg/kg) which reduced body fat content, increased energy expenditure, and reduced fasting insulin and 30-min insulin response to oral glucose tolerance test
- 12.5 mg/kg THCV caused a significant reduction in liver triglycerides.

(Jadoon KA, et al. Diabetes Care. 2016)

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Terpenes

- To date, there is over 200 terpenes/terpenoids detected in cannabis
- Terpenes account for 3-5% of the dry mass of the inflorescence.
- Have been found to have potential for bioactivity against both infectious and chronic health conditions
- Employed for thousands of years for therapeutic purposes such as anti-inflammatory, anti-microbial, antioxidant, anti-cancer and anti-diabetic.
- Provide the foundation of the flavor and aroma of the plant
- More prevalent terpenes include limonene, β-caryophyllene, linalool, humulene, ocimene, bisabolol, and terpinolene.

(Chacon, FT, 3 et al. 2022; Nuutinen, T. 2018; Kozioł A, et al. 2014)

Beta Caryophyllene

- β-caryophyllene (βCP), is one of the major sesquiterpenes found in cannabis
- Also present in clove, rosemary, black pepper, and lavender
- To date, studies have shown that βCP may display anticancer properties as well as anti-inflammatory properties
- Mice dosed with βCP displayed anxiolytic behaviour in the elevated plus maze and light dark test
- βCP to decrease latency to sleep and increased duration of sleep time

(Johnson A, et al. 2022; Gertsch J. 2008; Fidyt K, et al. 2016; Nuutinen T. 2018; Galdino PM, et al. 2012)

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Flavonoids

- It is estimated that cannabis has up to 10% of its plant compounds made up of flavonoids with up to 3% by weight in dried leaves and buds.
- Approximately 12 of the basic cannabis flavonoids can be found to some degree in the majority of strains
- Cannabis contains its own flavonoids exclusive to the cannabis species (cannaflavins A, B and C)
- Cannaflavins were first discovered by a researcher in London in 1986, Marilyn Barrett at the University of London.
- Anthocyanins are the flavonoid known to produce some of the more spectacular colors of cannabis are blues, purples, reds, and pinks

(Atkins P. 2020)

Table II: Flavonoid groups and important functional groups (7)

Major Flavonoid Groups	Flavonoid Subgroups	Important Functional Groups
Major flavonoids	Anthoxanthins	Flavones Flavonols
	Flavanones	Flavanones
	Flavanonols	Flavanonols
	Flavans	Flavanols Flavandiols Proanthocyanidins Anthocyanidins
Isoflavonoids	Isoflavonoids	Isoflavones Isoflavanes
Neoflavonoids	Neoflavones	Neoflavones
	Neoflavenes	Neoflavenes
Minor flavonoids	Aurones	Aurones Auronols
	Chalcones	Chalcones Hydroxycalcones

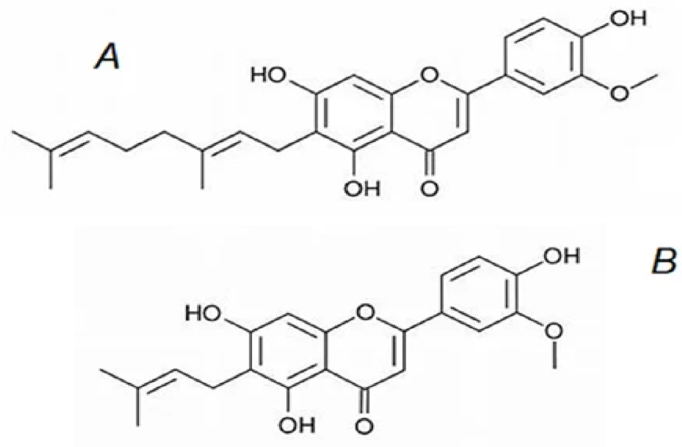

Figure 5: Cannaflavin A and B structures.

Table III: Cannabis flavonoids

Cannabis Flavonoid	Group
Cannaflavins A, B, and C	Flavone
Vitexin	Flavone Glucoside
Isovitexin	Flavone
Apigenin	Flavone
Kaempferol	Flavonol
Quercetin	Flavonol
Orientin	Flavone
Luteolin	Flavone
Catechins	Flavonol

(Atkins P. 2020)

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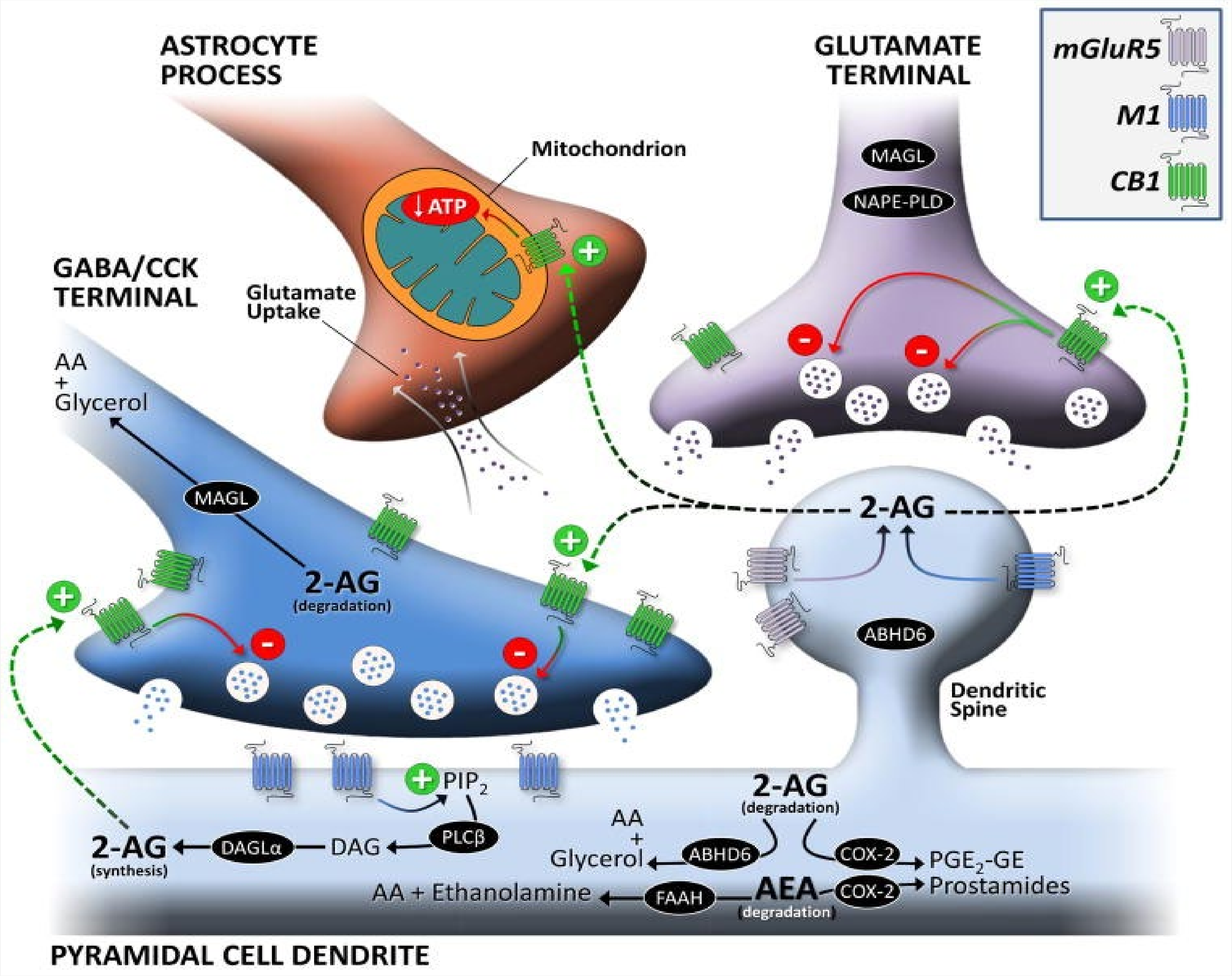
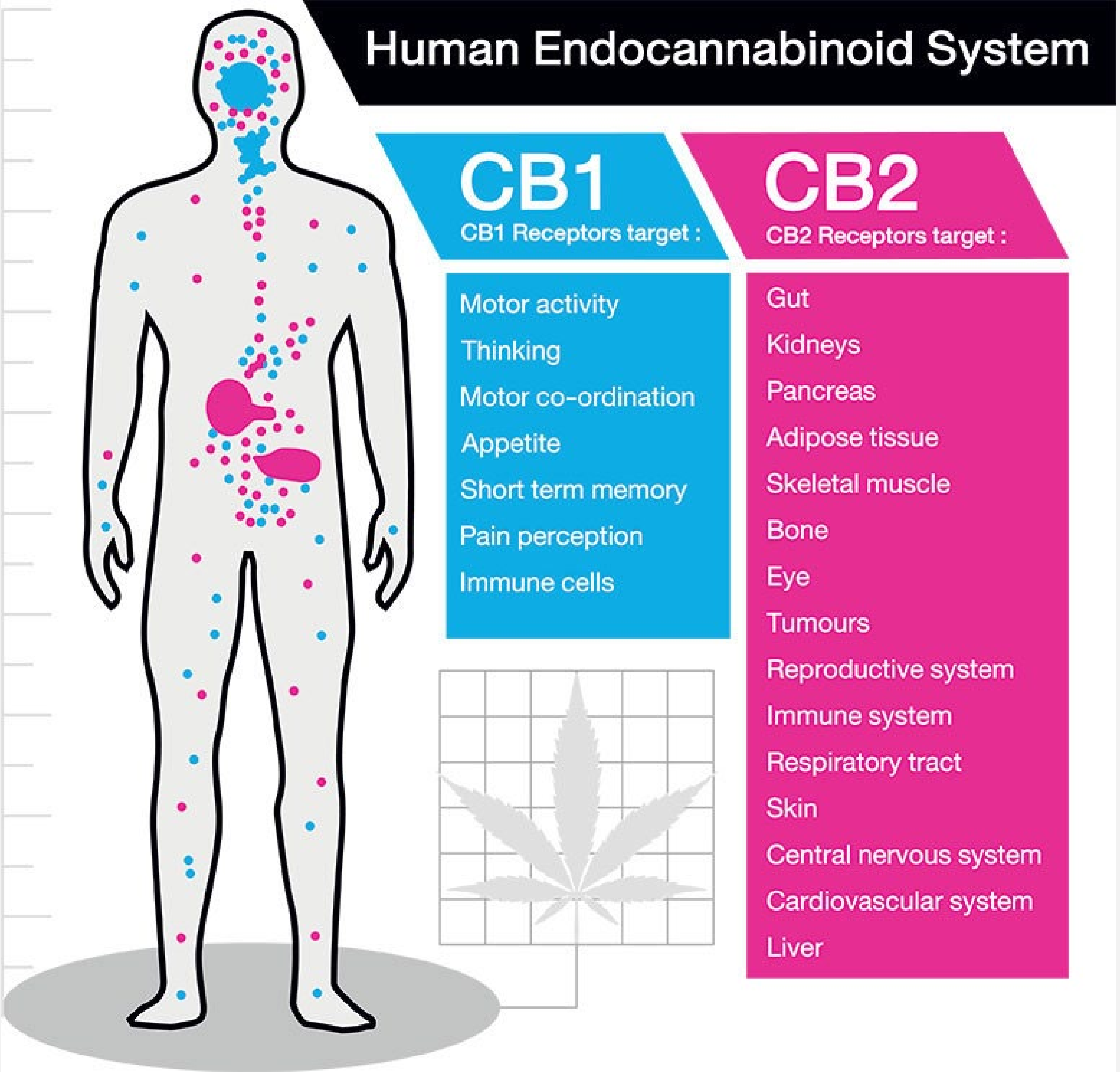
Endocannabinoids (ECS)

- The ECS is a widespread neuro-modulatory system that plays important roles in central nervous system development, synaptic plasticity, and the response to endogenous and environmental insults
- Comprised of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes responsible for the synthesis and degradation of the endocannabinoids
- Include CB1 and CB2 cannabinoid receptors, transient receptor potential (TRP) channels, and peroxisome proliferator activated receptors (PPAR's)
- The main endocannabinoids include 2-arachidonoyl glycerol (2-AG) and arachidonoyl ethanolamide (anandamide)
- N-acylethanolamines (NAE's) include PEA, SEA and OEA

- (Lu HC, Mackie K. Biol Psychiatry. 2016)



ASTROCYTE PROCESS
GLUTAMATE TERMINAL
mGluR5
M1
CB1
Mitochondrion
ATP
MAGL
NAPE-PLD
GABA/CCK TERMINAL
Glutamate Uptake
AA + Glycerol
MAGL
2-AG
(degradation)
2-AG
ABHD6
Dendritic Spine
PIP2
PLCβ
2-AG
(synthesis)
DAGLα
DAG
2-AG
(degradation)
AA + Glycerol
ABHD6
COX-2
PGE2-GE
AA + Ethanolamine
FAAH
AEA
(degradation)
COX-2
Prostamides
PYRAMIDAL CELL DENDRITE


Human Endocannabinoid System
CB1
CB1 Receptors target :
Motor activity
Thinking
Motor co-ordination
Appetite
Short term memory
Pain perception
Immune cells
CB2
CB2 Receptors target :
Gut
Kidneys
Pancreas
Adipose tissue
Skeletal muscle
Bone
Eye
Tumours
Reproductive system
Immune system
Respiratory tract
Skin
Central nervous system
Cardiovascular system
Liver

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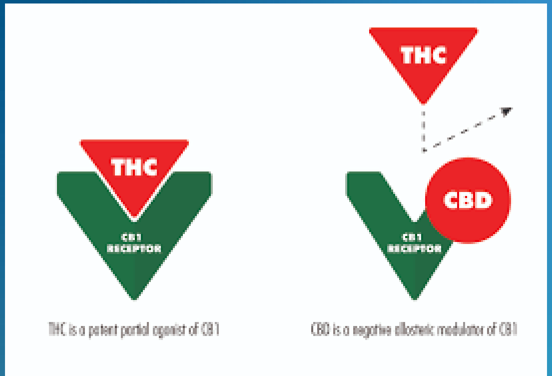
Interaction between Cannabis and Endocannabinoid system



- Partial agonists or antagonists at the prototypical cannabinoid receptors, CB1 and CB2
- CBD does not bind to CB1 receptors
- Daily cannabis use has been associated with a range of neuroadaptations in the endocannabinoid system
- Cannabis, particularly high THC variants have been found to down-regulate the brain CB1 receptor, which reverses after ~2–14 days of abstinence as well as reduce levels of fatty acid amide hydroxylase (FAAH; 14%−20%), the enzyme that metabolizes anandamide and is the primary regulator of its signaling in the brain
- Currently, we have a very limited understanding of the impact of most cannabis constituents on the endocannabinoid system.

(Hanney M. 2022)

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Drugs made from Cannabis

- Whole plant cannabis drugs are based mainly on ratios of THC and CBD
- Extensive research is being conducted on cultivars and genetics that can increase the amount of certain cannabinoids and terpenes to occur naturally in plants
- Minor cannabinoids and terpenes are now being researched and drugs are now starting to appear on the market
- Delivery methods, bioavailability, combinations that are best for certain conditions and specific cultivars are currently being investigated.
- This plant provides many opportunities for drug development in many areas.

Thank you so much for your time

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