

Cannabis Chemistry and Bioactivity

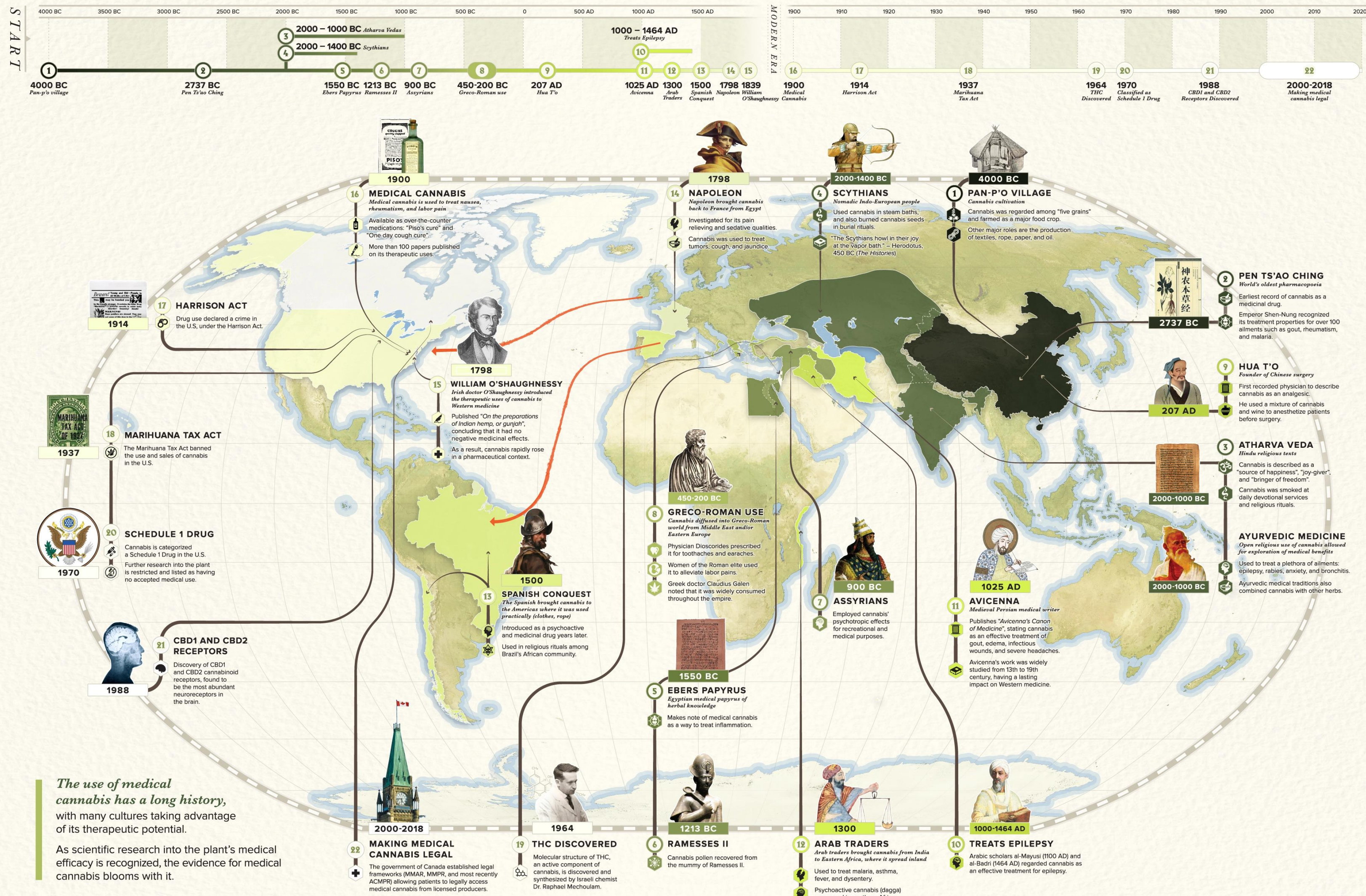
Stephanie Forscher-Dancause, Ph.D., Associate Teaching Professor, URI

RI CCC meeting, Sept 29, 2023

a 6,000 YEAR HISTORY of CANNABIS

THE CANNABIS SPACE IS HIGHLY POLARIZED TODAY.

However, it's less known that the plant has over 6,000 years of documented history – and its therapeutic applications appear to have been realized by most cultures. With medical cannabis making a comeback around the world, it's worth tracing the plant's humble beginnings and how it played a vital role throughout the centuries.



The use of medical cannabis has a long history, with many cultures taking advantage of its therapeutic potential.

As scientific research into the plant's medical efficacy is recognized, the evidence for medical cannabis blooms with it.

Sources: • A Historical Geography of Cannabis. Dr. Barney Warf, Geographical Review 104 (4), © 2014 American Geographical Society of New York.
• History of Medical Cannabis. Andrew Hand (MSc) et al., Journal of Pain Management 9 (4), © 2016 MedReleaf Corp. and Nova Science Publishers, Inc.
• Cannabis: A Complete Guide. Dr. Ernest Small © 2016 CRC Press.

~ 5,000 years ago

- ❖ The oldest known record of the medicinal use of cannabis comes from the original *Pen Ts'ao*.
- ❖ Chinese pharmacopeia lists hundreds of medicines derived from plant, animal, and mineral sources.
- ❖ Written by the Chinese emperor Shen Nung in 2737 BCE, though no original texts remain in existence.
- ❖ Shen Nung is called the "father of Chinese medicine."
- ❖ The first surviving version of the text dates to 300-200 BCE and contains uses of *ma*, the Chinese word for cannabis, in the treatment of fatigue, rheumatism, malaria, eczema/psoriasis, and inflammatory disease.

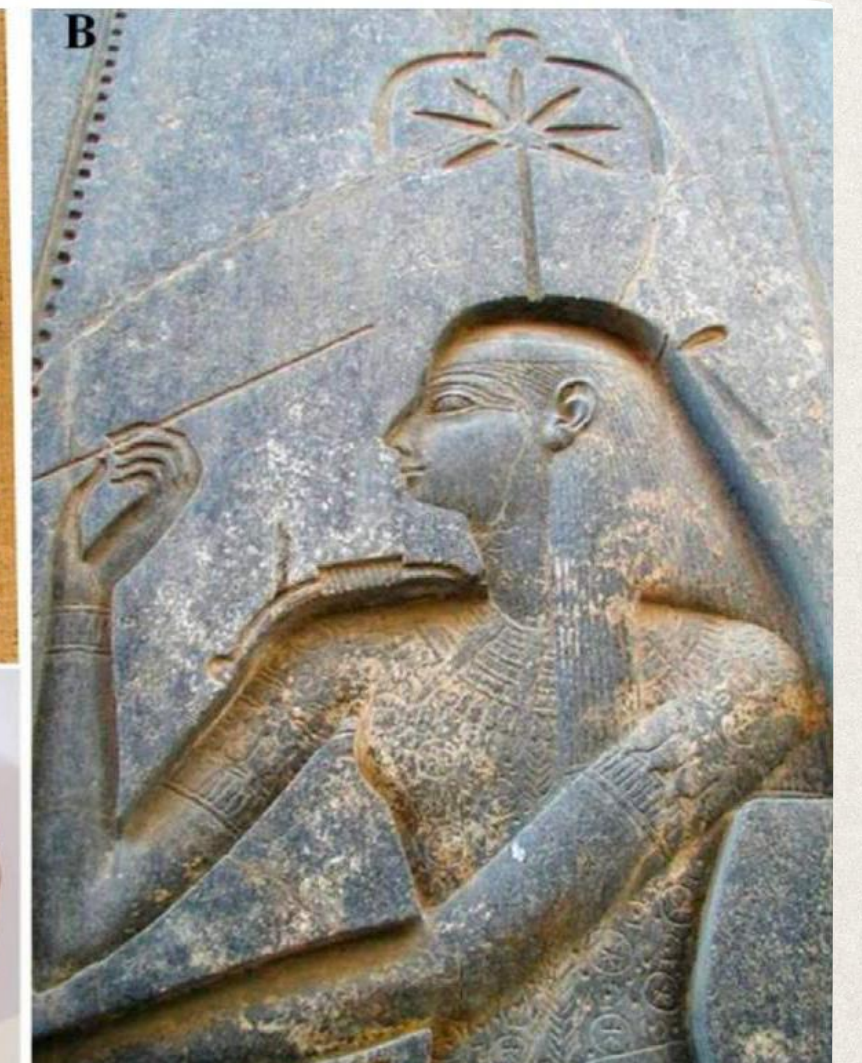
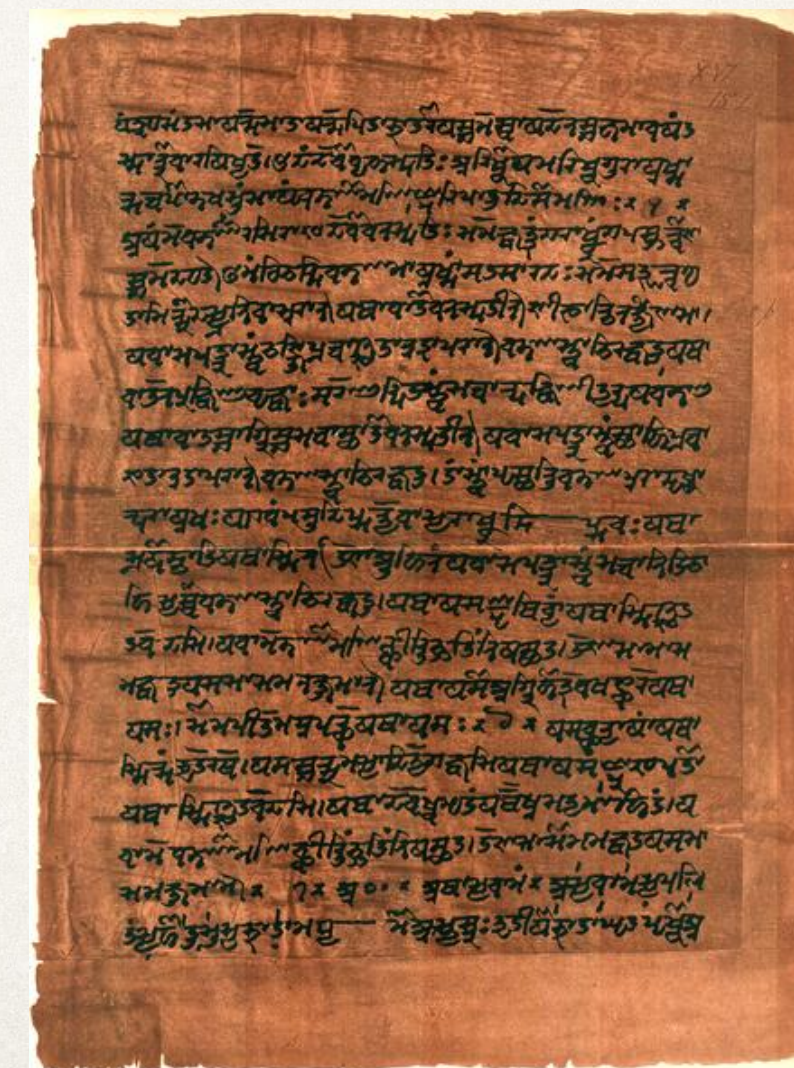


~ 3,500 - 4,000
years ago

- ❖ The use of cannabis for religious purposes is first found in India.
- ❖ Bhang, ganja, and charas were used for religious rituals as well as socially.
- ❖ Ayurvedic medicine details the use of cannabis for the treatment of anxiety, rabies, and epilepsy among others.
- ❖ The species name *Cannabis indica* arose from the prevalence of cannabis and its use in India, though it is actually the same species as *Cannabis sativa*.

~ 3,000 years ago

- ❖ Both the Egyptian Ebers Papyrus (ancient text detailing herbal medicines) and the Assyrian clay tablets detail the medicinal use of cannabis.



~ 2,000 years ago
(3rd century)

- ❖ In 207 CE, the first report of cannabis being used as an analgesic (painkiller) comes from Chinese surgeon Hua Tuo.
- ❖ During surgery, he would use a mixture of cannabis resin and wine as an anesthetic.



15th century

- ❖ While the use of cannabis initially spread west from China, India, and the Middle East into Europe, its use was halted when its medicinal use was banned by the Spanish Inquisition.
- ❖ The use of cannabis was abandoned by European physician when Pope Innocent VIII criminalized its medicinal use, calling cannabis an instrument of the devil.



Reintroduction to western medicine (1830s)

- ❖ William O'Shaughnessy, British physician working in India
- ❖ The plant, traditional texts, and local doctors
 - ❖ Bhang: paste of dried leaves - mixed with peppery/spice drinks or boiled with milk and sugar to make majoon (sweets)
 - ❖ Gunjah: resinous flower buds - smoked
 - ❖ Charas: resin scraped from buds - most potent and costly
- ❖ Animal Studies
 - ❖ to prove safety and determine dose O'Shaughnessy began studies in stray dogs before moving to several animals including cats, goats, fish, vultures, and storks.
 - ❖ No deaths, even at the highest doses, all animals recovered with no apparent harm.

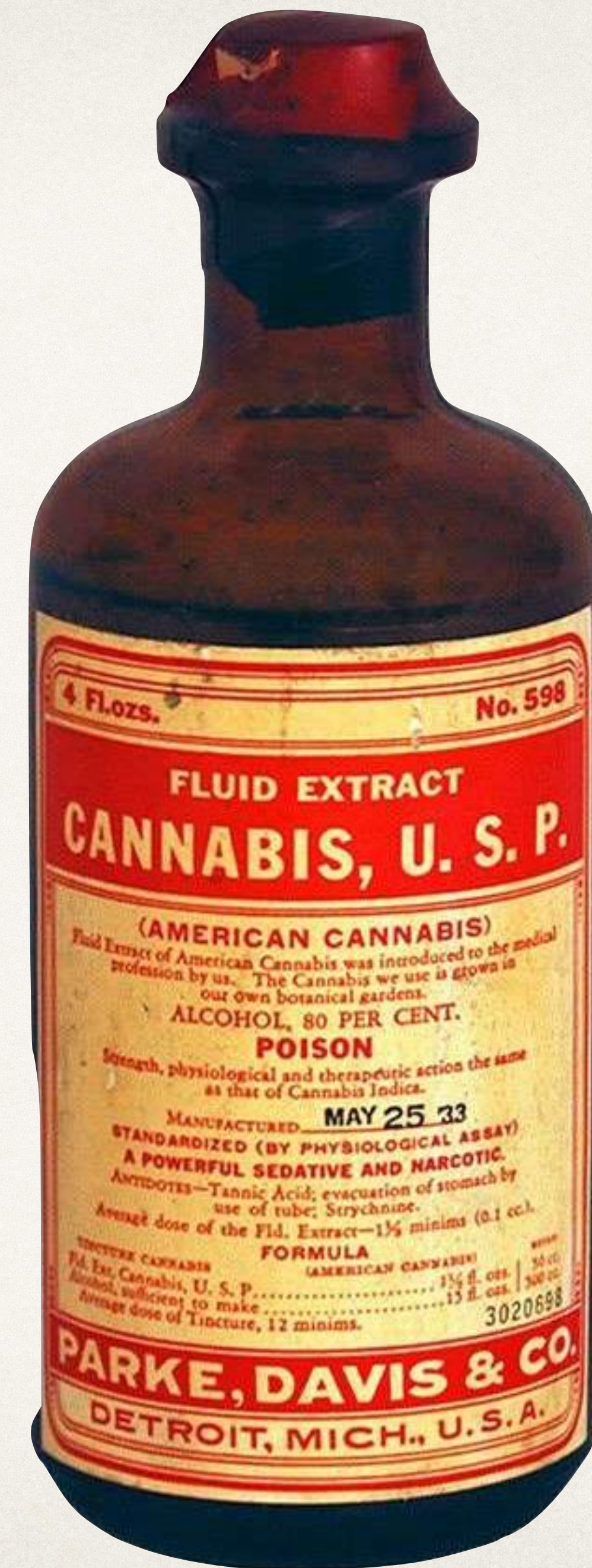


O'Shaughnessy's Human Studies

- ❖ Rheumatism - 3 subjects were given a "modest dose" of cannabis resin in alcohol; subjects "were not only uninjured by the narcotic, but much relieved of their rheumatism" and "quite cured" at discharge three days later
- ❖ Rabies - he knew it wouldn't be a cure but found that with frequent doses of cannabis "the awful malady was stripped of its horrors"
- ❖ Cholera - cannabis stopped the vomiting and diarrhea which attenuated extreme dehydration allowing patients to recover
- ❖ Tetanus - life threatening disease characterized by muscle rigidity and powerful muscle spasms; cannabis relaxed muscles and stopped the spasms; results "seems unequivocally to show that when given boldly and in large doses the resin of hemp is capable of arresting effectually the progress of this formidable disease"

Late 1800s - early 1900s

- ❖ Western medicine embraced the medicinal use of cannabis
- ❖ Listed on US Pharmacopeia from 1850-1942
- ❖ 1892 - Canadian physician, Sir William Osler, "father of modern medicine," calls cannabis the best treatment for migraines in *The Principles and Practice of Medicine* (considered the first textbook for internal medicine)



Cannabis prohibition

- ❖ Advances in pharmacology/organic chemistry allowed for isolation of active compounds, preference for standardized single compound medicines
- ❖ Legislation banning cannabis
 - ❖ Marijuana Tax Act 1937 – main opponent against act was the American Medical Association
 - ❖ UN Single Convention of Narcotic Drugs - placed cannabis in most restricted category
 - ❖ Controlled Substances Act 1971 - classified cannabis as a schedule 1 drug
 - ❖ High potential for abuse, no accepted medical use, and a lack of accepted safety even under medical supervision

HHS rescheduling recommendation

- ❖ On August 29, 2023, the Department of Health and Human Services (HHS) recommended to the DEA that marijuana be rescheduled from Schedule I to Schedule III under the Controlled Substances Act (CSA).
- ❖ Schedule III – a drug, chemical, or substance with a moderate to low potential for physical and psychological dependence and a lower abuse potential than Schedule II
 - ❖ Includes drugs such as those containing > 90 mg of codeine/dosage unit (ex: Tylenol with codeine), ketamine, anabolic steroids, testosterone

Ethnobotany and Pharmacognosy

Derived from Greek words “pharmakon” (drug) and “gnosis” (knowledge)

Natural Product Medicines

- ❖ Newman and Cragg, J. Nat. Prod. 2020, 83, 770-803
- ❖ All approved drugs (1981-2019)
- ❖ If we look at everything except the orange slice, we can see that natural products make up about 75% of new drugs over the past 40 years!

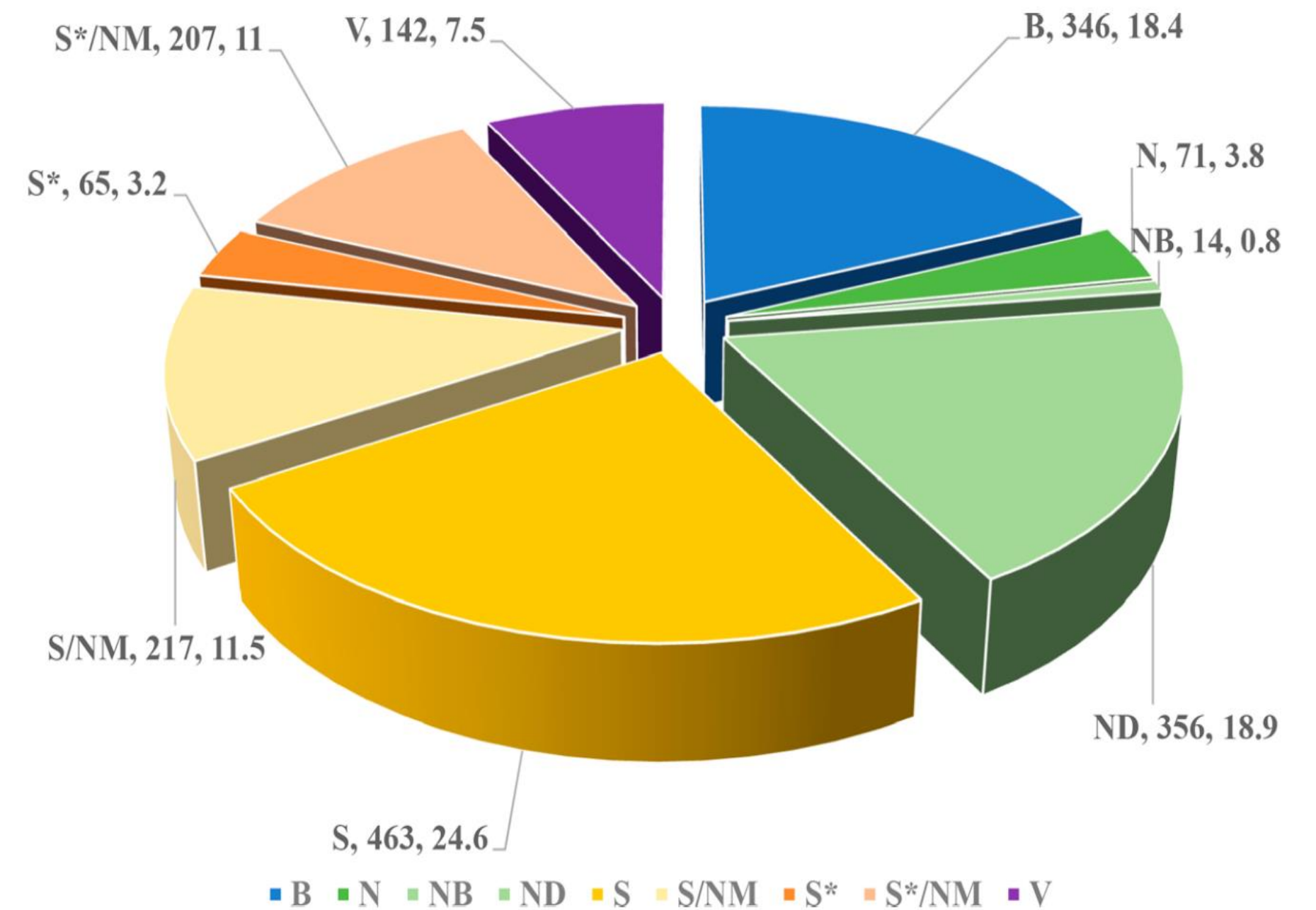
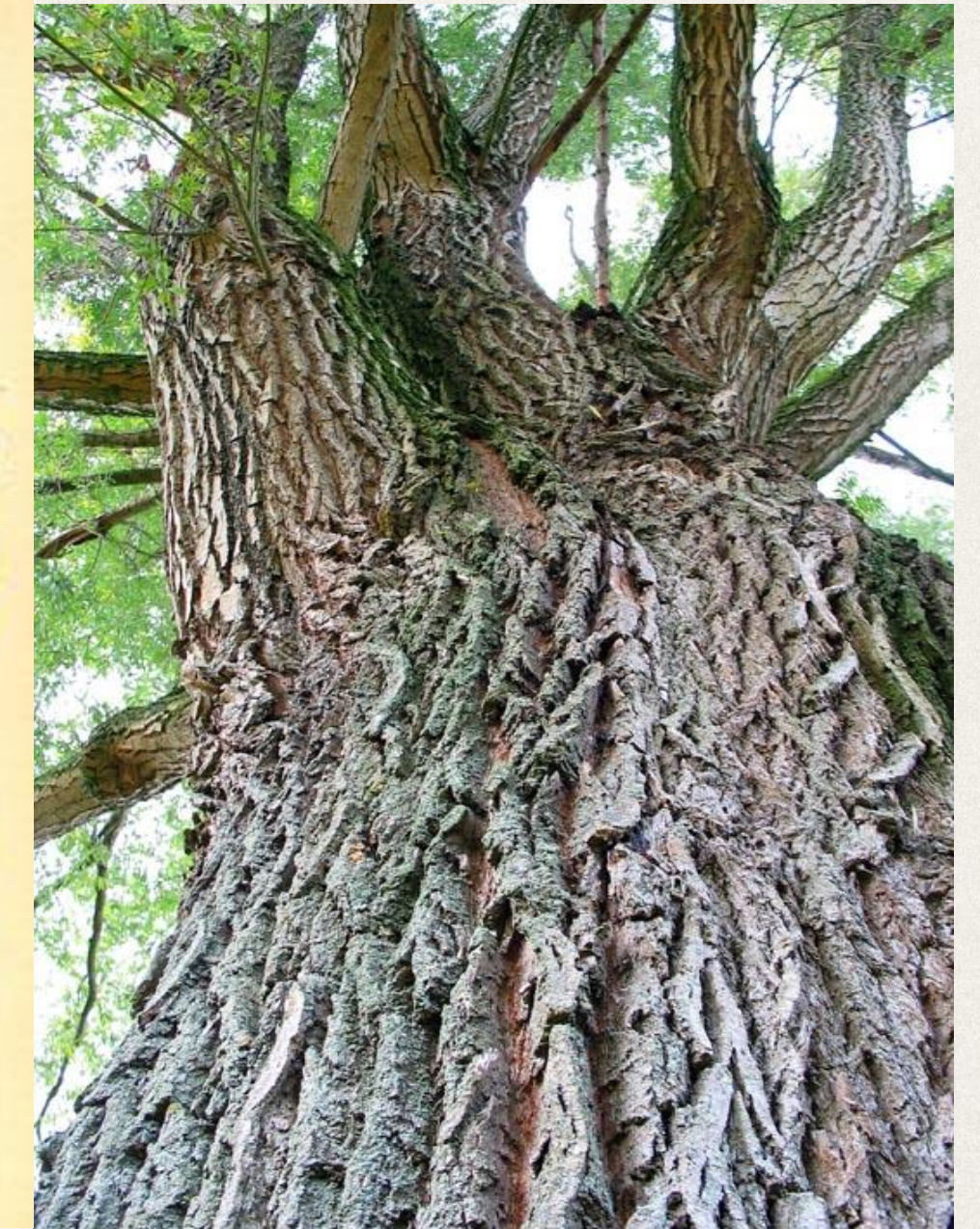


Figure 1. All new approved drugs 01JAN81 to 30SEP19; n = 1881.

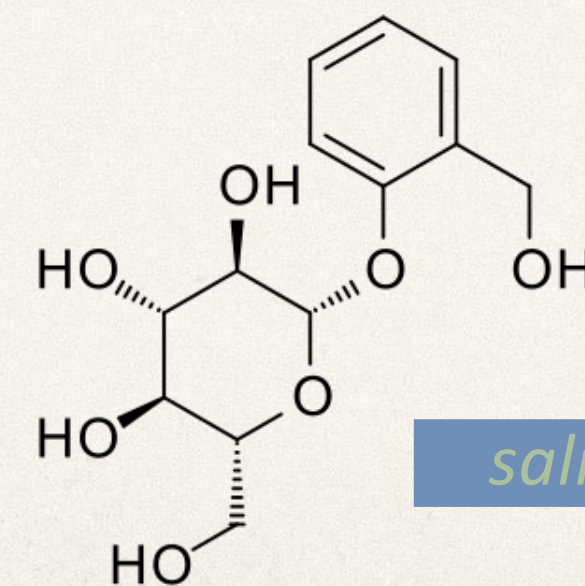
code	brief definition/year
B	biological macromolecule, 1997
N	unaltered natural product, 1997
NB	botanical drug (defined mixture), 2012
ND	natural product derivative, 1997
S	synthetic drug, 1997
S*	synthetic drug (NP pharmacophore), 1997
V	vaccine, 2003
/NM	mimic of natural product, 2003

Salicin: Willow tree bark

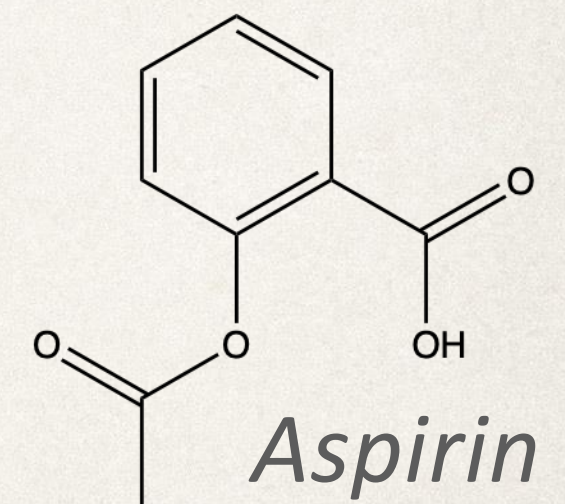
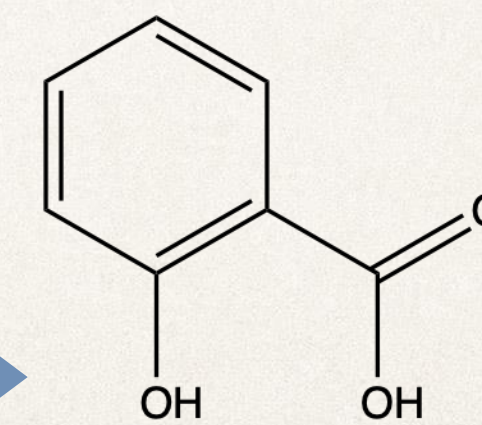
- ❖ Anti-inflammatory use dates back 1000s of years
- ❖ Hippocrates – 400 BC noted that it eased pain and reduce fever
- ❖ Late 1800s – was used to develop aspirin
- ❖ Some studies show willow is as effective as aspirin for reducing pain and inflammation (but not fever), and at a much lower dose
- ❖ Most likely due to other compounds in the bark



Salicin



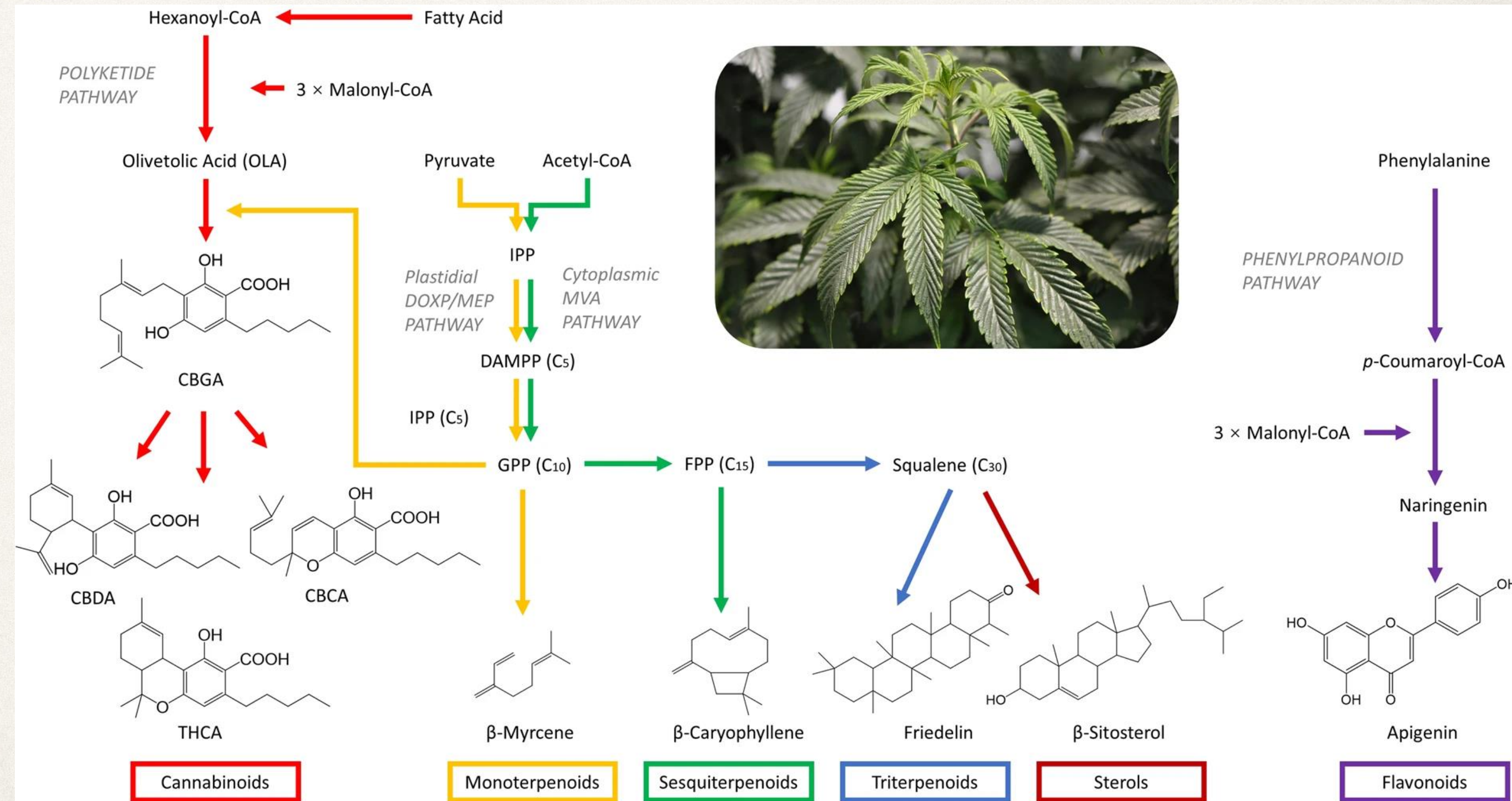
Salicylic acid



Cannabis Natural Products

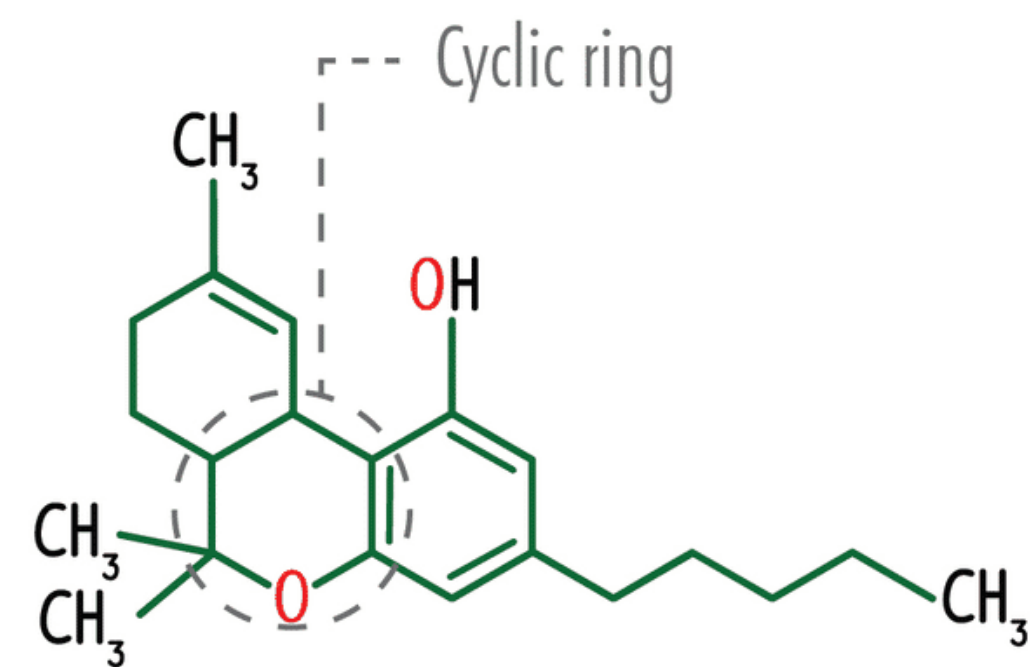


- ❖ Diverse and interesting chemistry
- ❖ Over 140 phytocannabinoids
 - ❖ Only a handful have begun studies
- ❖ Over 100 terpenes
 - ❖ Not exclusive to cannabis
- ❖ Flavonoids
 - ❖ Absent from seeds & roots



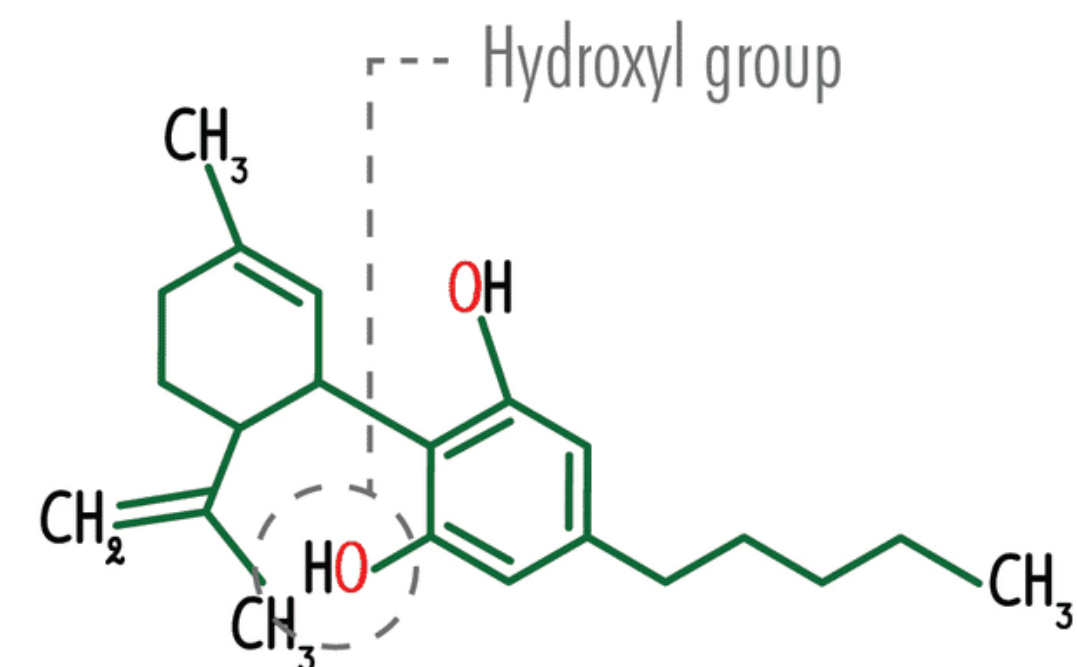
Phytocannabinoids

- ❖ Main bioactive constituents of cannabis: THC and CBD
 - ❖ Just two of over 140 cannabinoids produced by the plant



Tetrahydrocannabinol (THC)

Psychoactive constituent



Cannabidiol (CBD)

Non-psychoactive

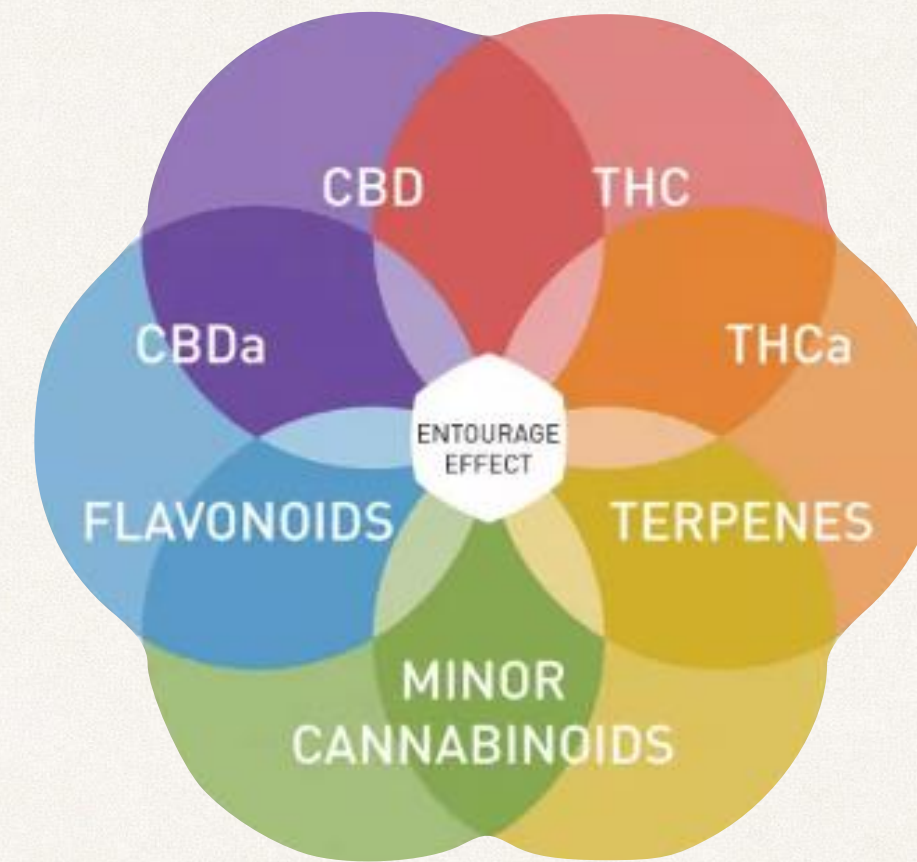
2018 Farm Bill - Legalization of “hemp”

- ❖ Multiple different strains of the same plant
- ❖ Government defined separation
- ❖ Hemp - cannabis with $< 0.3\%$ THC
 - ❖ Plant and it's extracts (CBD) are deschedule
- ❖ Marijuana - cannabis with $> 0.3\%$ THC
 - ❖ Remains a schedule I controlled substance, including CBD



Synergistic activities of cannabis metabolites

- ❖ Whole plant preparations vs. purified cannabinoid
- ❖ Often desired by patients
- ❖ Example of traditional medicine vs western medicine
- ❖ Polypharmacology
 - ❖ Target multiple receptors or complementary mechanisms which have similar/synergistic biological activity
 - ❖ Adds in many difficult variable to assess in dosing and efficacy



The Entourage Effect

History



1998:
Shimon Ben Shabbat **notices:**
Potential synergy in body-molecules that interact with the ECS



1999:
Raphael Mechoulam and Shimon Ben Shabbat **suggest:**
This synergy "may play a role in the widely held (but not experimentally based) view that in some cases plants are better drugs..."



2001:
Elizabeth Williamson **presents:**
The synergistic benefits of cannabis vs isolated THC

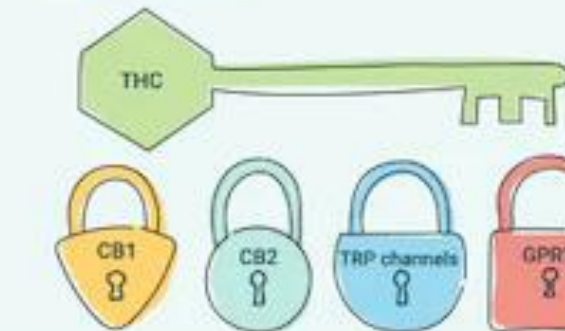


2011:
Ethan Russo **writes:**
Taming THC, which suggests cannabinoid and terpene synergy in cannabis

Mechanisms

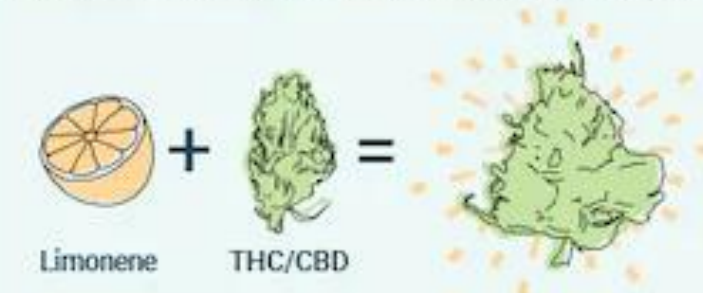
1. Multi-target enhancing effects

Molecules can bind to several receptors thereby enhancing effects (e.g. THC binds to CB1 & CB2 receptors, and also interacts with select GPRs & TRP channels).



2. Molecular movement enhancing effects

Molecules which are inactive by themselves may enhance the effects of active molecules by altering their movement through the body (e.g. Cannabinoids absorption through the lungs could be improved by the presence of bronchodilating terpenes such as limonene or pinene).



3. Modulating adverse effects

Molecules can interact to neutralize or reduce side effects (e.g. CBD can modulate the adverse effects of THC).



“The whole is greater than the sum of its parts.”

- Aristotle

Criticism

There's some criticism about the enhancing effect aspects of the theory, suggesting there's not enough evidence to support it. But this seems to be mostly related to lack of research. For now, the jury is still out.

References:

*From gan-si-gun-nu to anandamide and 2-arachidonoylglycerol: the ongoing story of cannabis, Raphael Mechoulam, Shimon Ben-Shabat, 1998.

*Synergy and other interactions in phytomedicines, Elizabeth Williamson, 2001.

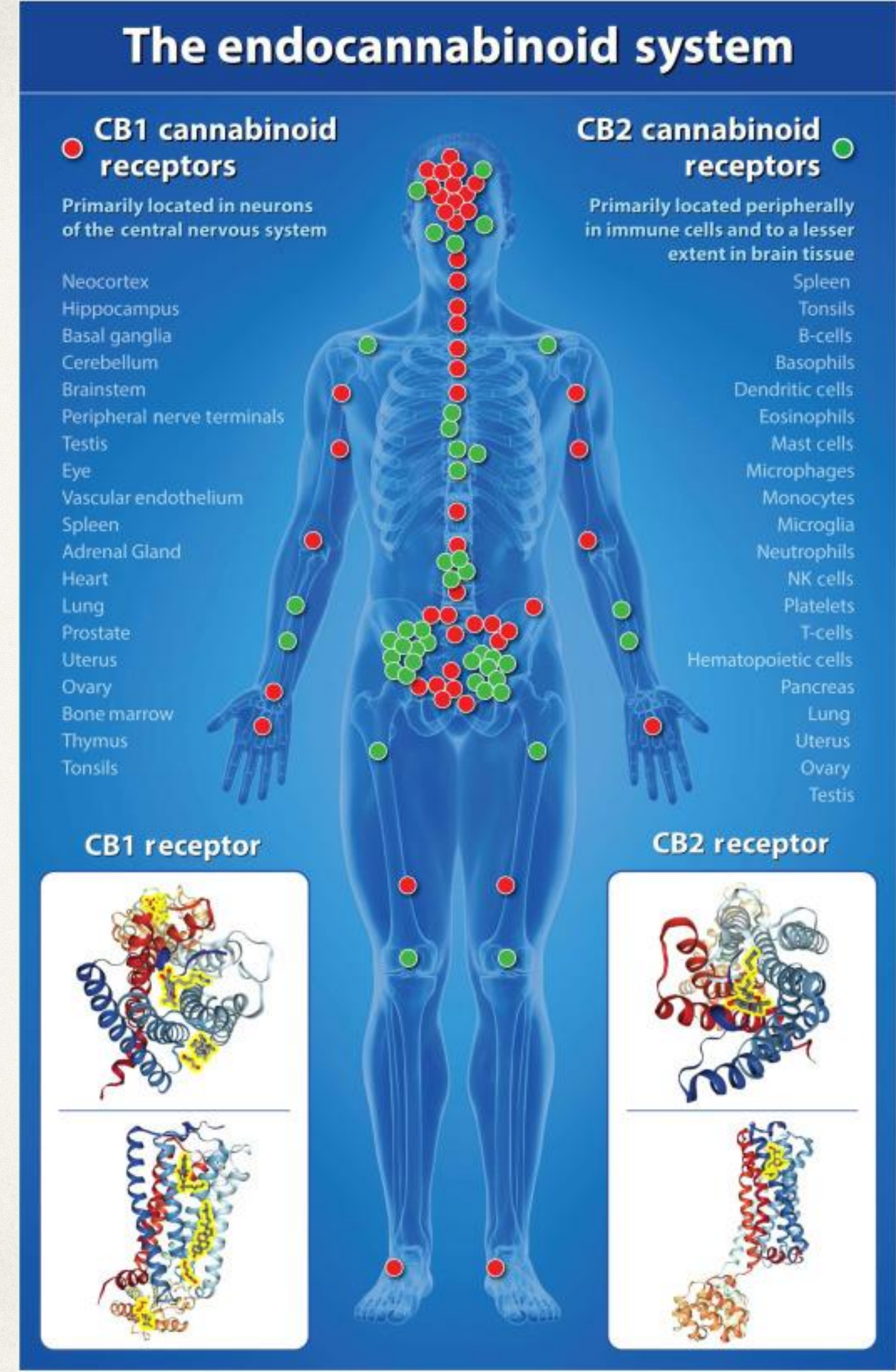
*Synergy research: Approaching a new generation of phytopharmaceuticals, Hildebert J. Wagner, Gudrun S. Ulrich-Merzenich, 2009.

*Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects, Ethan Budd Russo, 2011.

How does cannabis produce its effects?

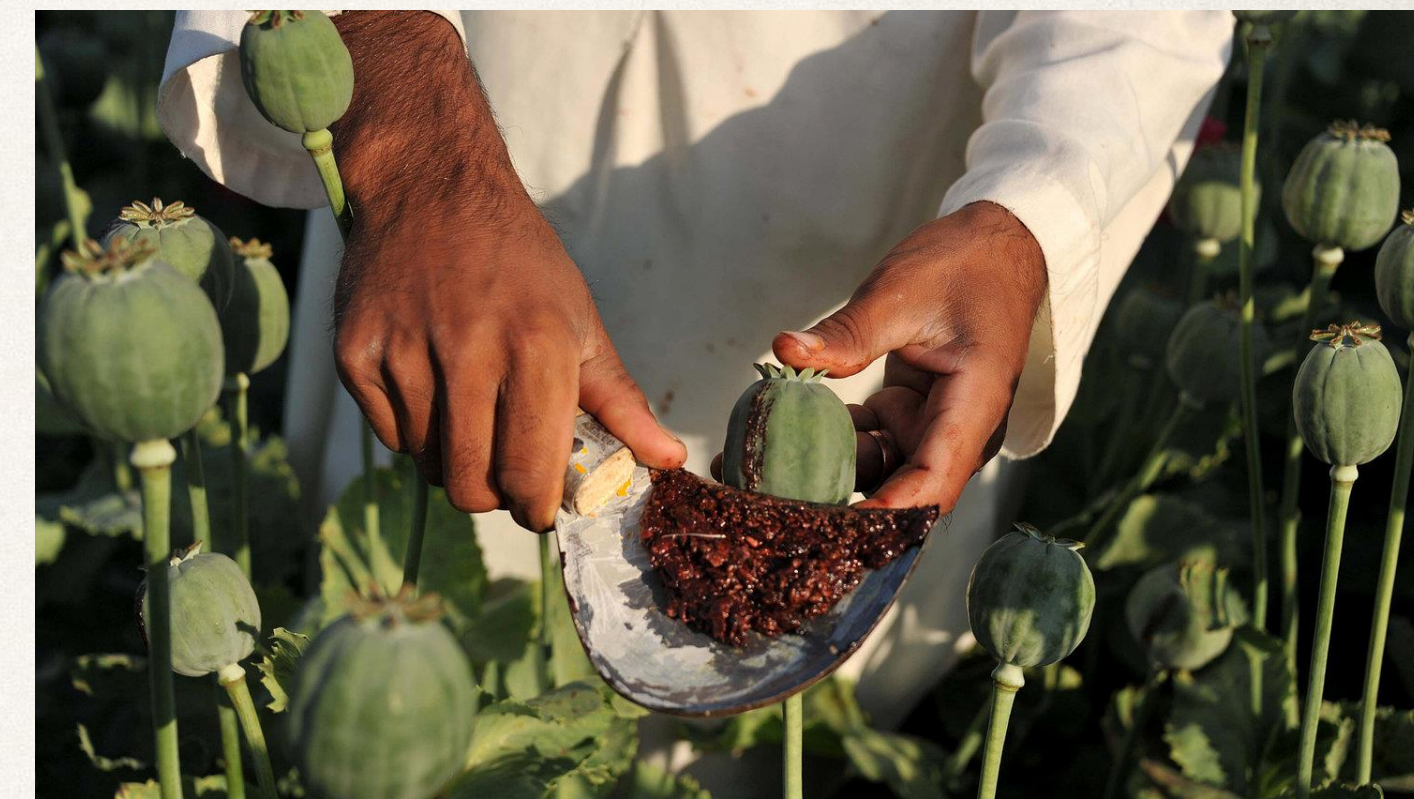
Discovery of the Endocannabinoid System

- ❖ The cannabinoids were discovered in the 1930s-40s. Structures were elucidated in the 1960s.
- ❖ Question remains: How does cannabis have its effects?
 - ❖ 1988 & 1993 - discovery of the cannabinoid receptor 1 (CB₁) and cannabinoid receptor 2 (CB₂)
 - ❖ 1992 - discovery of endogenous cannabinoids (endocannabinoids)
 - ❖ N-arachidonylethanolamine, coined anandamide - ananda, Sanskrit word meaning bliss + amide
 - ❖ Endogenous ligand for CB₁ receptor,
 - ❖ Controls a cascade of reactions in the cell that regulate a staggering array of functions when turned on.
 - ❖ A second endocannabinoid, 2-arachidonoyl glycerol, was later found



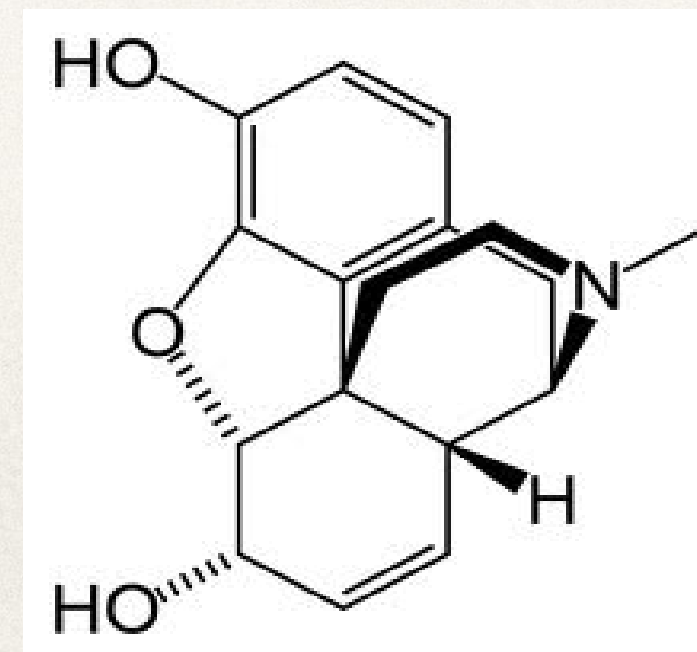
Discovery of novel physiology from the study of plant metabolites is not uncommon

- ❖ Ex: Opioids and Endogenous opioids
- ❖ Natural opioids (poppy) - Morphine, codeine
- ❖ Semi-synthetic- Oxycodone, Hydrocodone, Heroin; Synthetic - Fentanyl
- ❖ Endogenous opioids
 - ❖ Endorphin (endogenous morphine)
- ❖ Act on μ -opioid receptors – critical role in pain processing, stress response/regulation, immune functions

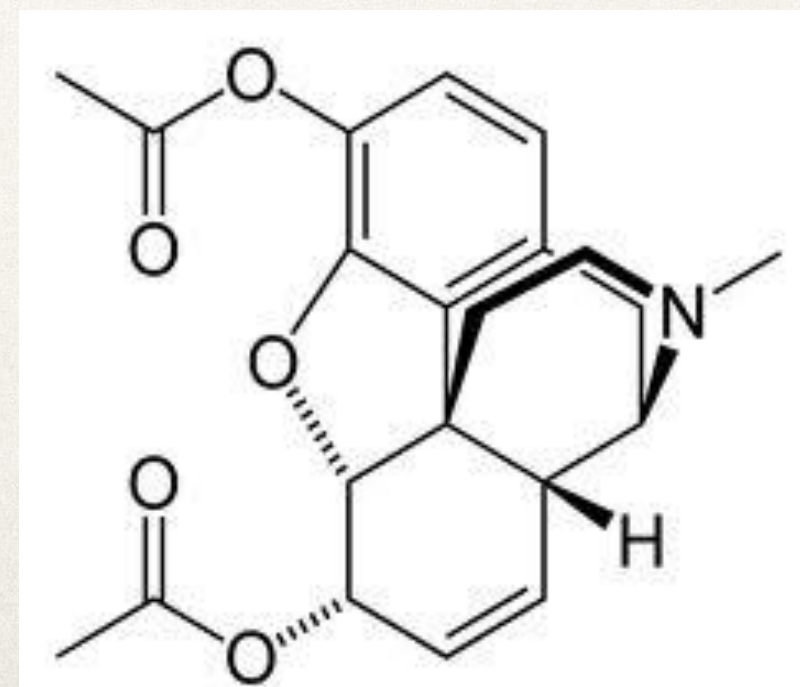


Noorullah Shirzada/AFP/Getty Images

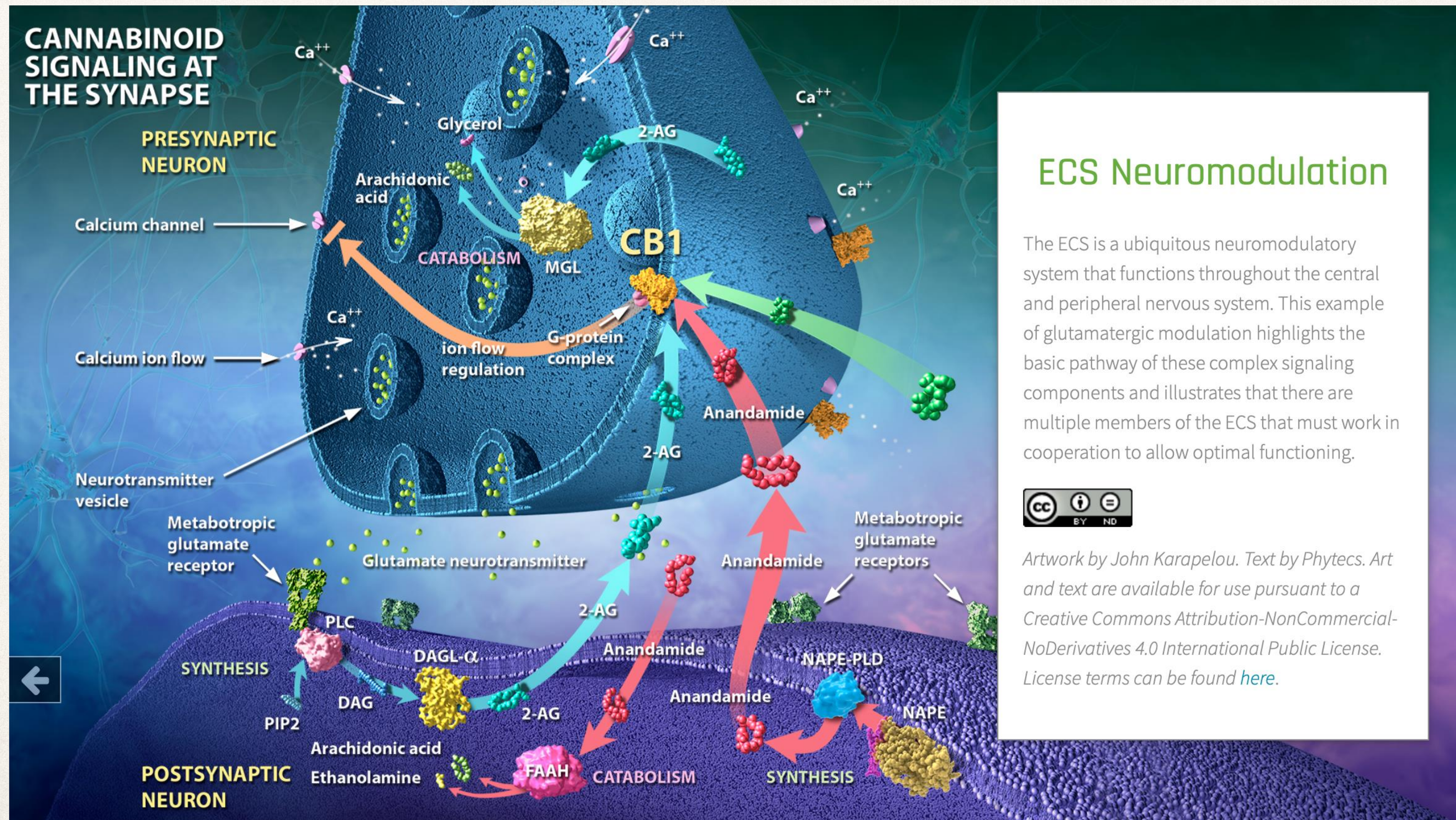
Morphine



Heroin



How does the endocannabinoid system function?



ECS Neuromodulation

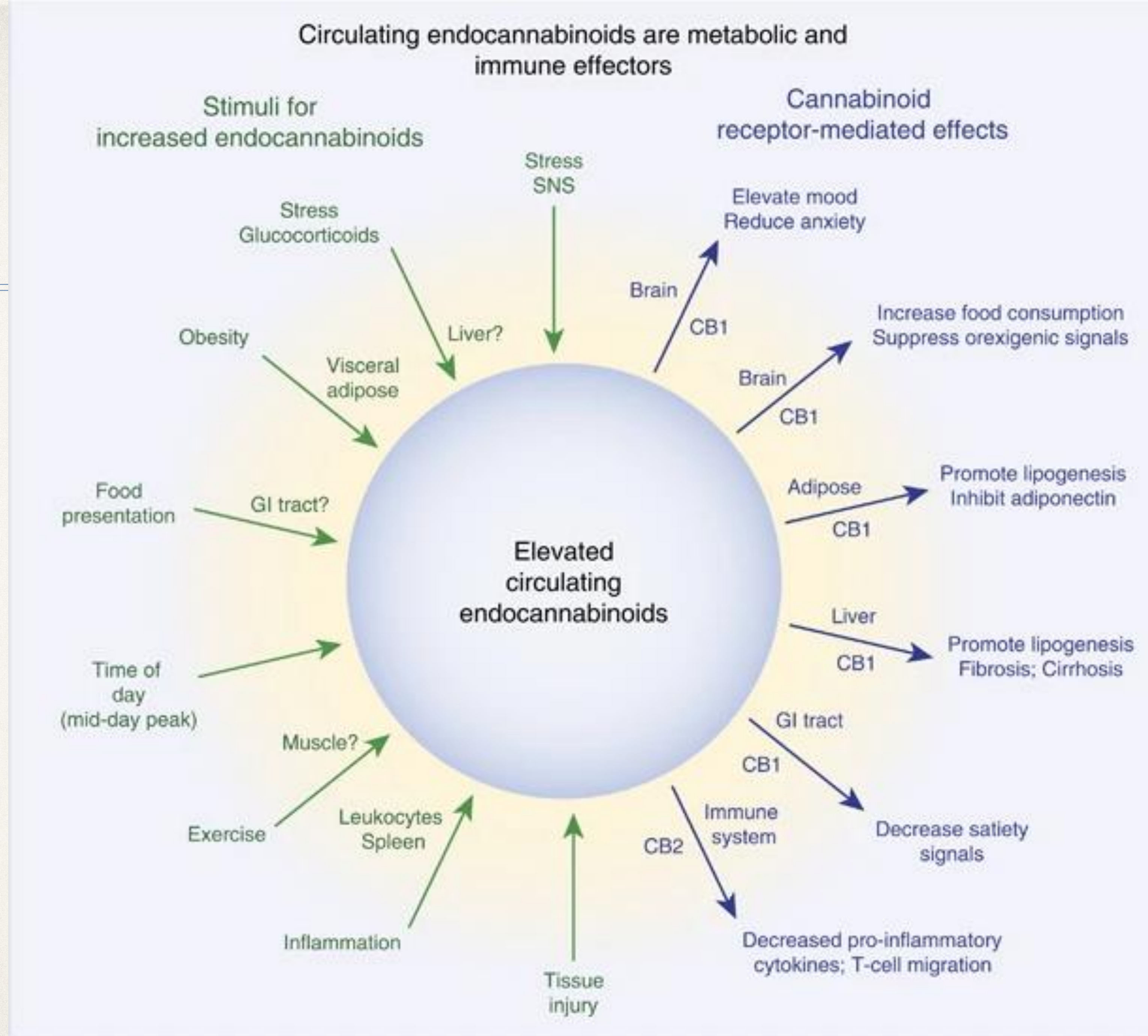
The ECS is a ubiquitous neuromodulatory system that functions throughout the central and peripheral nervous system. This example of glutamatergic modulation highlights the basic pathway of these complex signaling components and illustrates that there are multiple members of the ECS that must work in cooperation to allow optimal functioning.



Artwork by John Karapelou. Text by Phytects. Art and text are available for use pursuant to a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International Public License. License terms can be found [here](#).

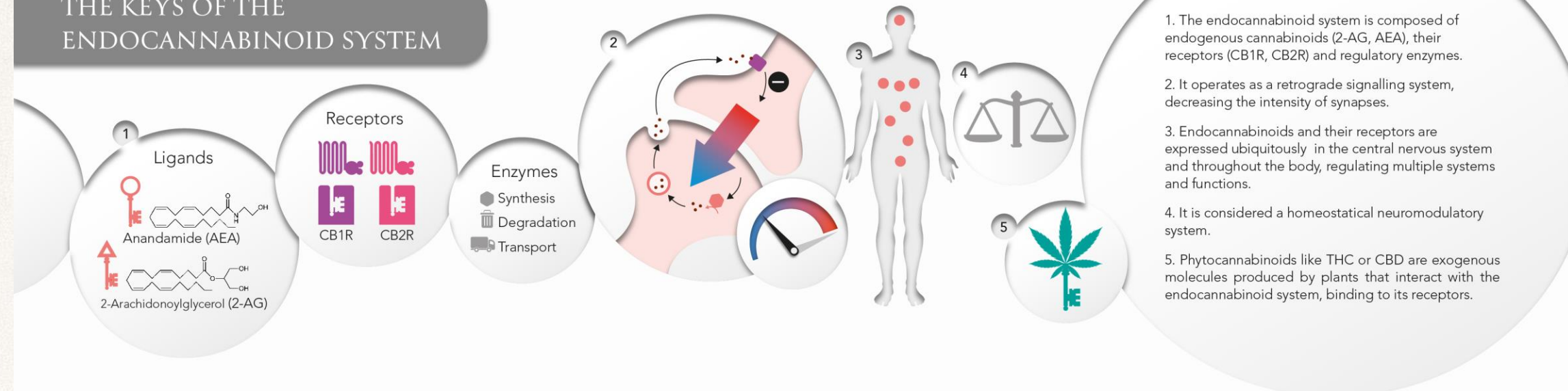
Endocannabinoid System

- ❖ Activation of CB receptors is implicated in cellular homeostasis
- ❖ CB1 are mainly localized in the CNS and peripheral nervous system
 - ❖ Modulation of neurotransmitter release at the presynaptic neuron
- ❖ CB2 are mainly located peripherally in organs and on immune cells
 - ❖ Involved in immunological responses and in the control of inflammation

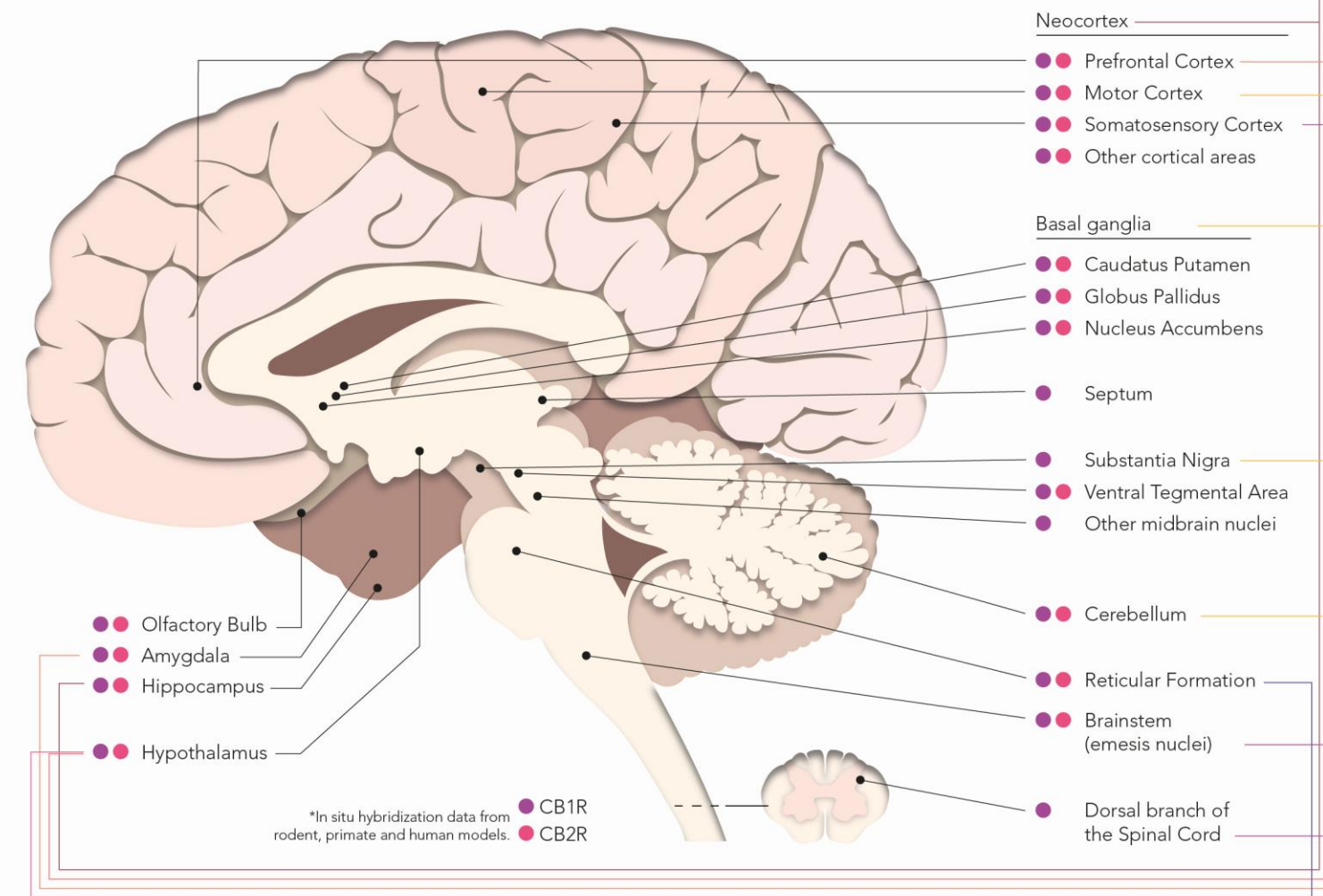
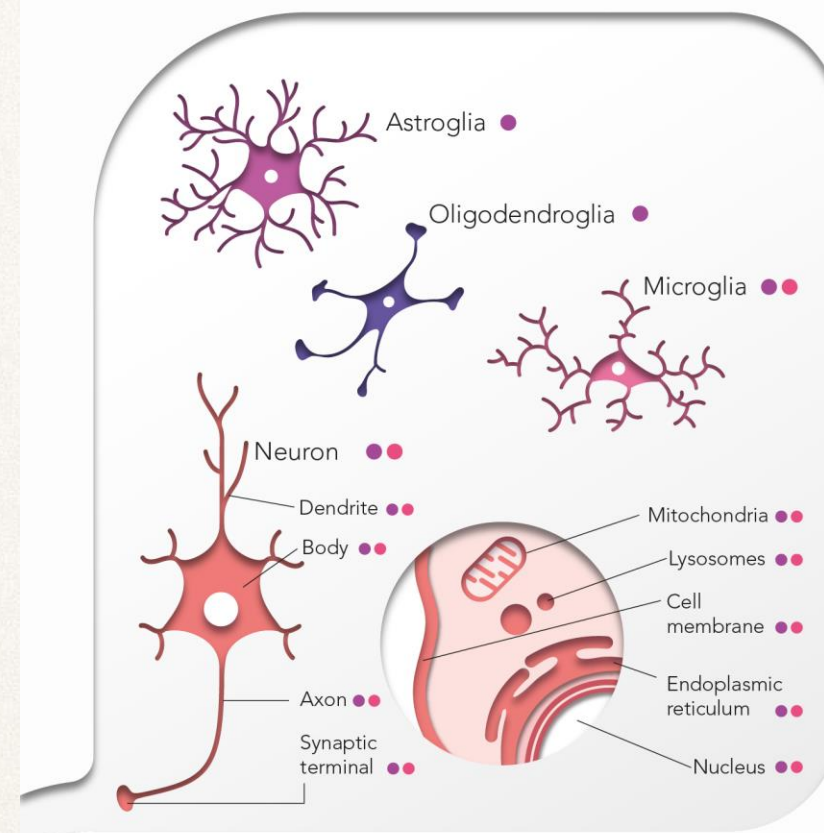


ENDOCANNABINOIDS IN THE CENTRAL NERVOUS SYSTEM

THE KEYS OF THE ENDOCANNABINOID SYSTEM



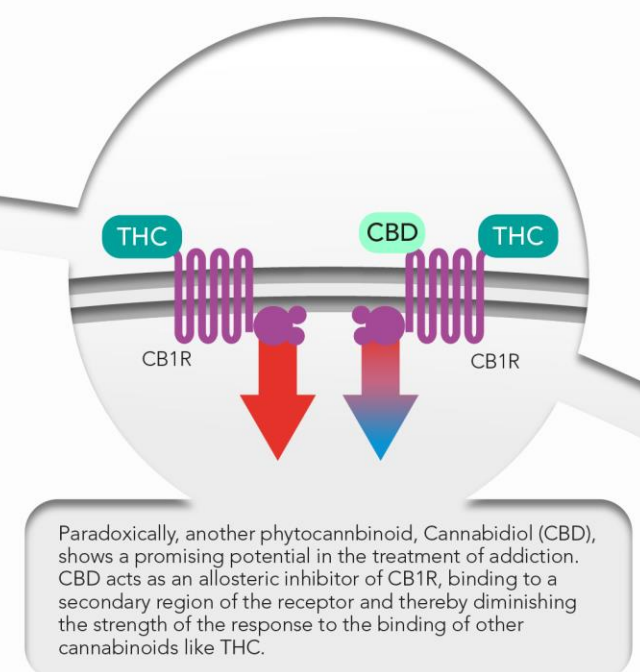
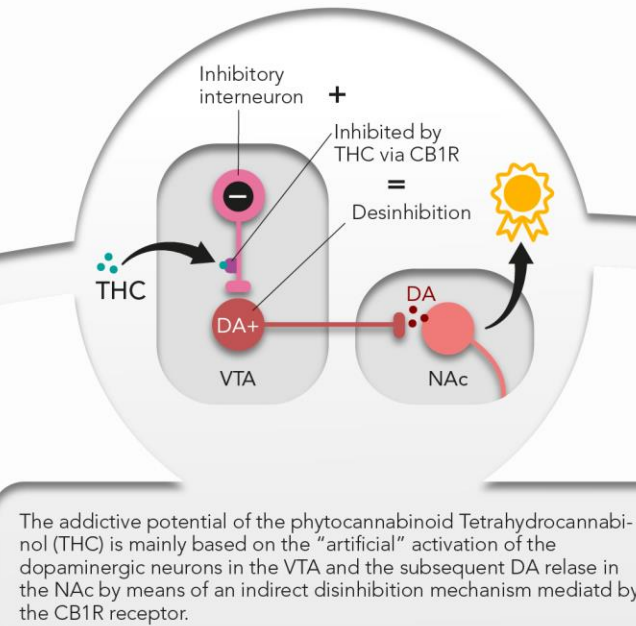
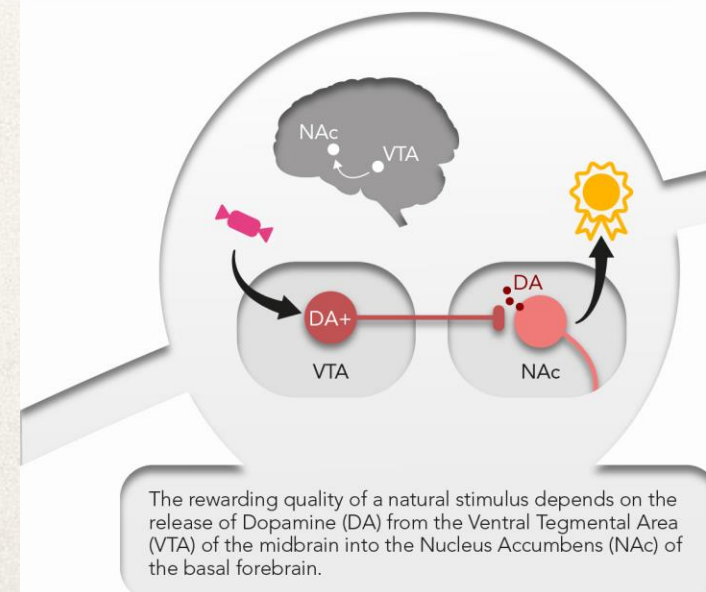
ENDOCANNABINOID RECEPTOR EXPRESSION



CENTRAL ACTIONS OF THE ENDOCANNABINOID SYSTEM

- Memory**
Promotes the extinction of old memories.
Stimulates hippocampal neurogenesis.
- Learning**
Regulates multiple plasticity processes:
Promotes Long Term Depression (LTD), inhibits Long Term Potentiation (LTP).
- Stress**
Promotes the habituation of the Hypothalamus – Pituitary – Adrenal Axis against the repeated exposure to a stressant stimulus.
- Emotionality**
Inhibits the negative emotional assessment and the anxiety response to negative stimuli.
Important role in emotional pathologies (anxiety, depression, posttraumatic stress disorder).
- Locomotion**
Regulates motor learning, planning and execution.
Therapeutic potential in the treatment of motor symptoms of Parkinson's Disease.
- Nervous System development**
Regulates synaptogenesis and synaptic pruning during fetal development and neurogenesis in the adult Hippocampus.
- Food intake**
Increases appetite (central and peripheral regulation).
Crosstalk with dietary hormones (Leptin, Orexin, Ghrelin).
- Pain**
Inhibits major nociceptive pathways at a brain, spinal and peripheral (ganglionic and terminal) level.
- Inflammation**
Regulates inflammatory and immune responses.
Neuroprotector effect against excitotoxicity.
- Sleep**
Promotes deep and REM sleep direct- and indirectly (through the regulation of adenosina).

CANNABINOIDS, REWARD & ADDICTION



Zou & Kumar 2018. Int J Mol Sci. 13:19(3):833.
 Joshi & Onaivi 2019. Adv Exp Med Biol. 1162:1-12.
 Liu et al. 2009. Genes Brain Behav. 8(5):519-30.
 Mackie 2005. Handb Exp Pharmacol. (168):299-325.
 Chye et al. 2019. Front Psychiatry. 10:1063.
 Spanagel 2020. Dialogues Clin Neurosci. 22(3):241-250.
 Huang & Zhang 2016. Mol Med Rep. 14(4):2899-903.
 Di Marzo & Piscitelli 2015. Neurotherapeutics. 12(4):692-8.

“modulating Endocannabinoid System activity may have therapeutic potential in almost all diseases affecting human, including obesity/metabolic syndrome, diabetes and diabetic complications, neurodegenerative, inflammatory, cardiovascular, liver, gastrointestinal, skin diseases, pain psychiatric disorders, cachexia, cancer, chemotherapy induced nausea and vomiting, among others.”

*Pacher, P., & Kunos, G. (2013). Modulating the endocannabinoid system in human health and disease: successes and failures. FEBS Journal, 280(9), 1918-1943.
doi:10.1111/febs.12260*

FDA-approved cannabis pharmaceuticals

(red = synthetic, green = isolate)

- ❖ Dronabinol (US) (Marinol, Syndros)

- ❖ Synthetic THC; 2.5 – 10 mg capsules; 5 mg/mL solution
- ❖ Chemotherapy-induced nausea and vomiting; appetite stimulant for weight loss

- ❖ Nabilone (US) (Cesamet)

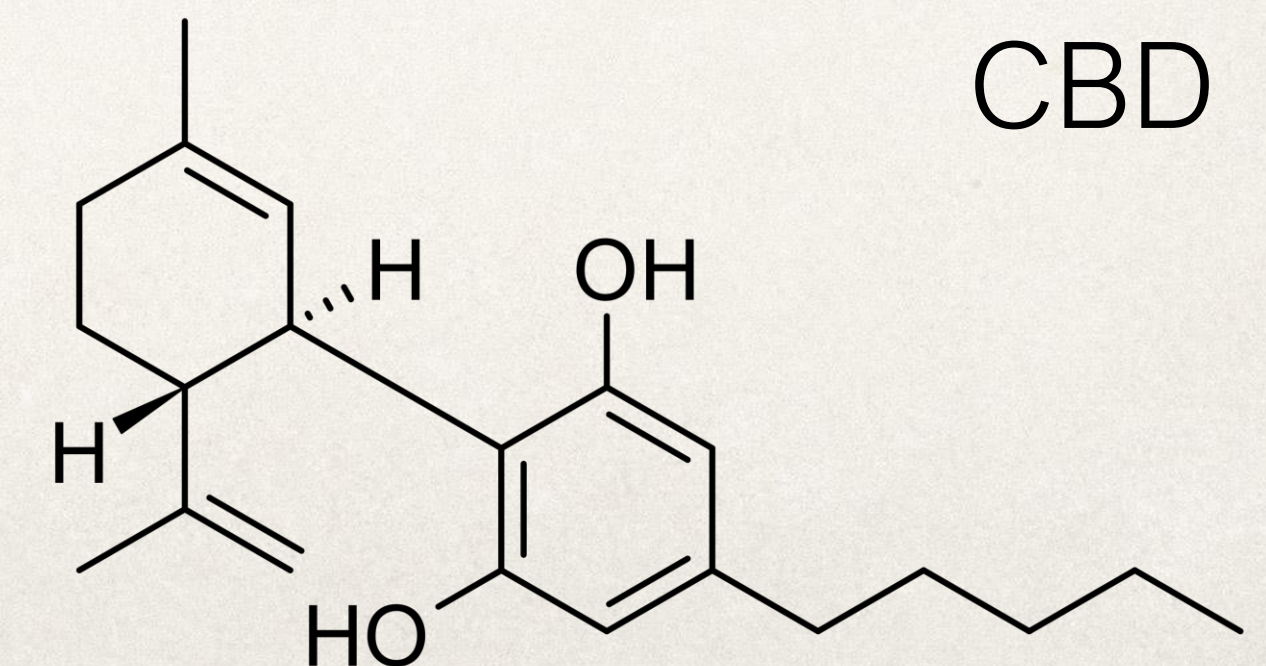
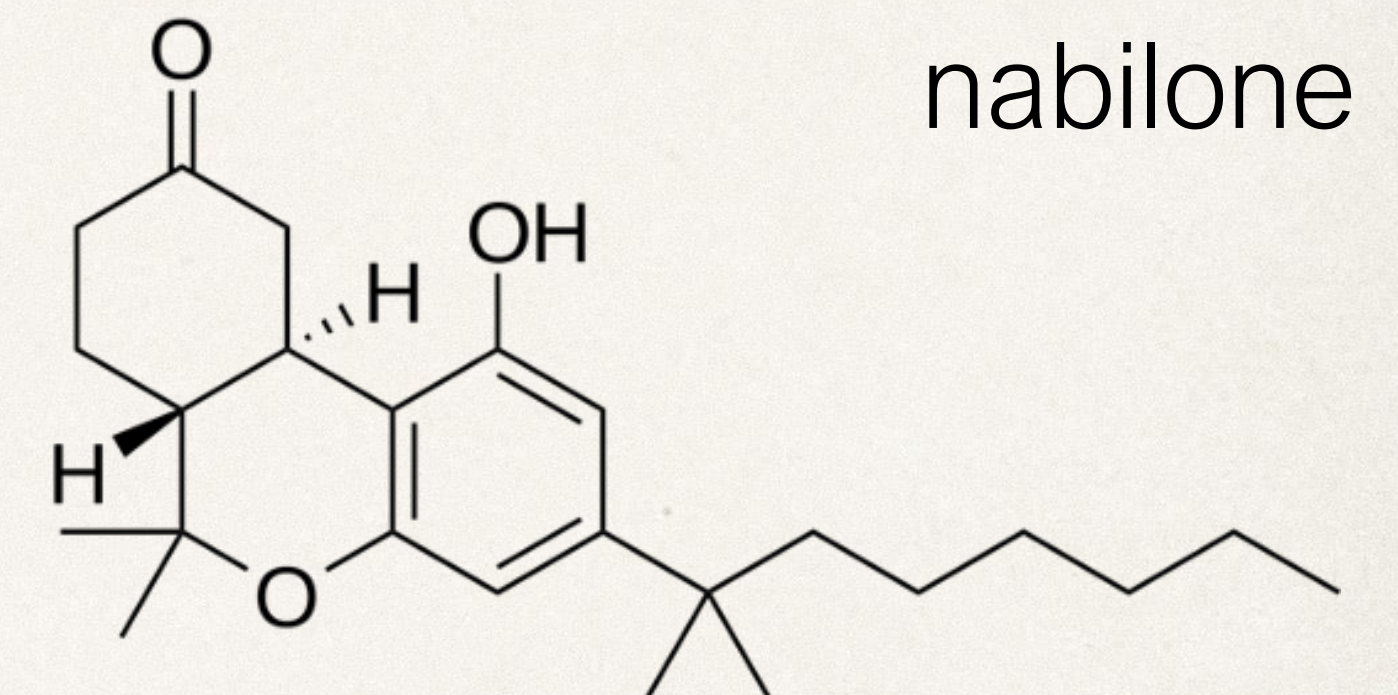
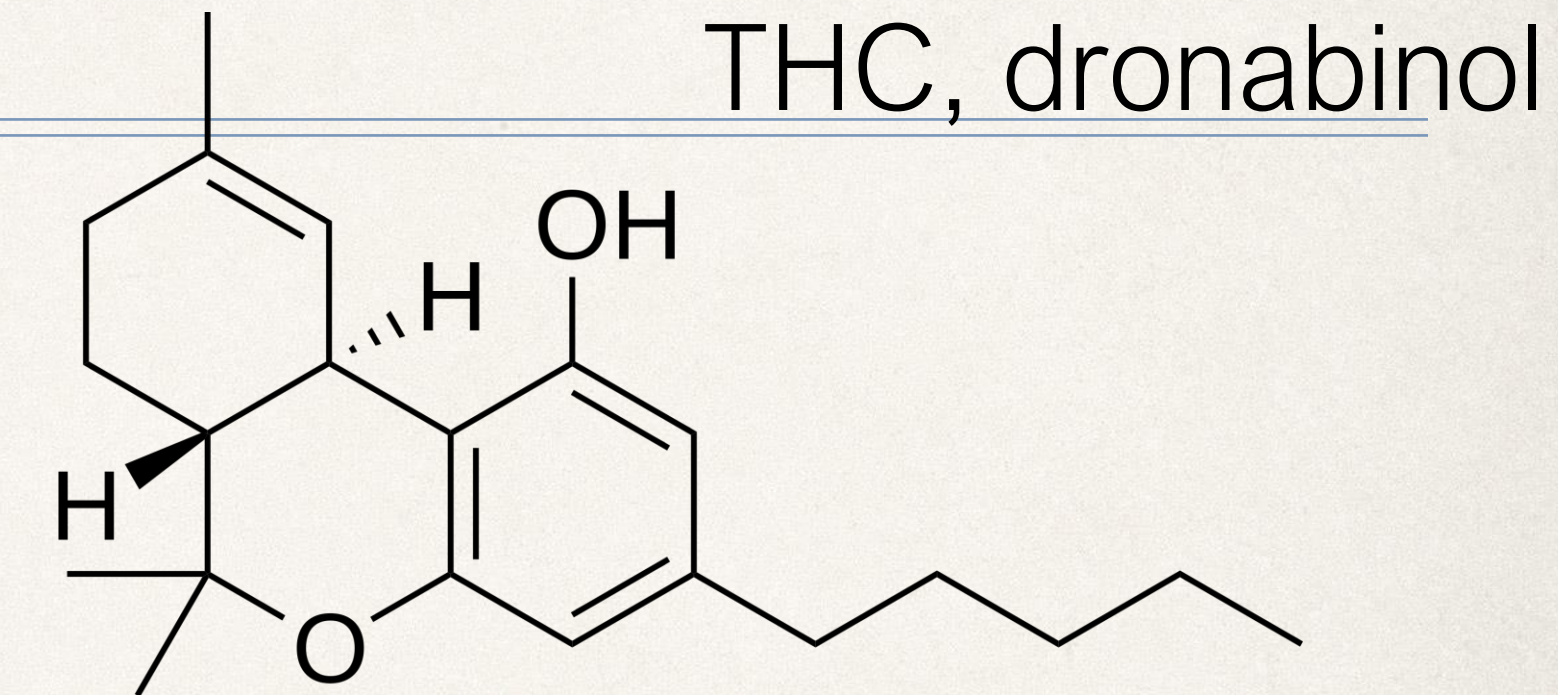
- ❖ Synthetic THC analog; 1 mg capsule
- ❖ Chemotherapy-induced nausea and vomiting

- ❖ Cannabidiol (US) (Epidiolex)

- ❖ 100 mg/mL oral solution
- ❖ Seizures from Dravet and Lennox-Gastaut syndromes, ≥ 2 years

- ❖ Nabiximols (Canada, EU) (Sativex)

- ❖ Sublingual spray ~ extract with 1:1 ratio of THC and CBD (2.5 mg)
- ❖ Neuropathic pain, MS symptoms



Pharmaceutical formulations

- ❖ Marinol (capsule)
- ❖ Dyndros (oral solution)
 - ❖ Easy to swallow alternative
 - ❖ Lower individual variability
- ❖ Cesamet (capsule)
- ❖ Nabiximols (sublingual spray)



FDA-approved drugs vs. medical cannabis/recreational products

- ❖ Medical Marijuana products

- ❖ Flower

- ❖ Extracts (solvent-based)

- ❖ Solventless extracts

- ❖ Edibles

- ❖ Vape oils



Evidence of cannabinoid treatments



Conclusive or substantial

- Chemotherapy-induced nausea and vomiting
- Chronic pain
- Epilepsy - intractable seizures in Dravet and Lennox-Gastaut syndromes
- Spasticity symptoms associated with MS




Moderate evidence

- Glaucoma - decreasing intraocular pressure
- Sleep disturbances associated with chronic pain, MS, fibromyalgia, and sleep apnea



Limited evidence

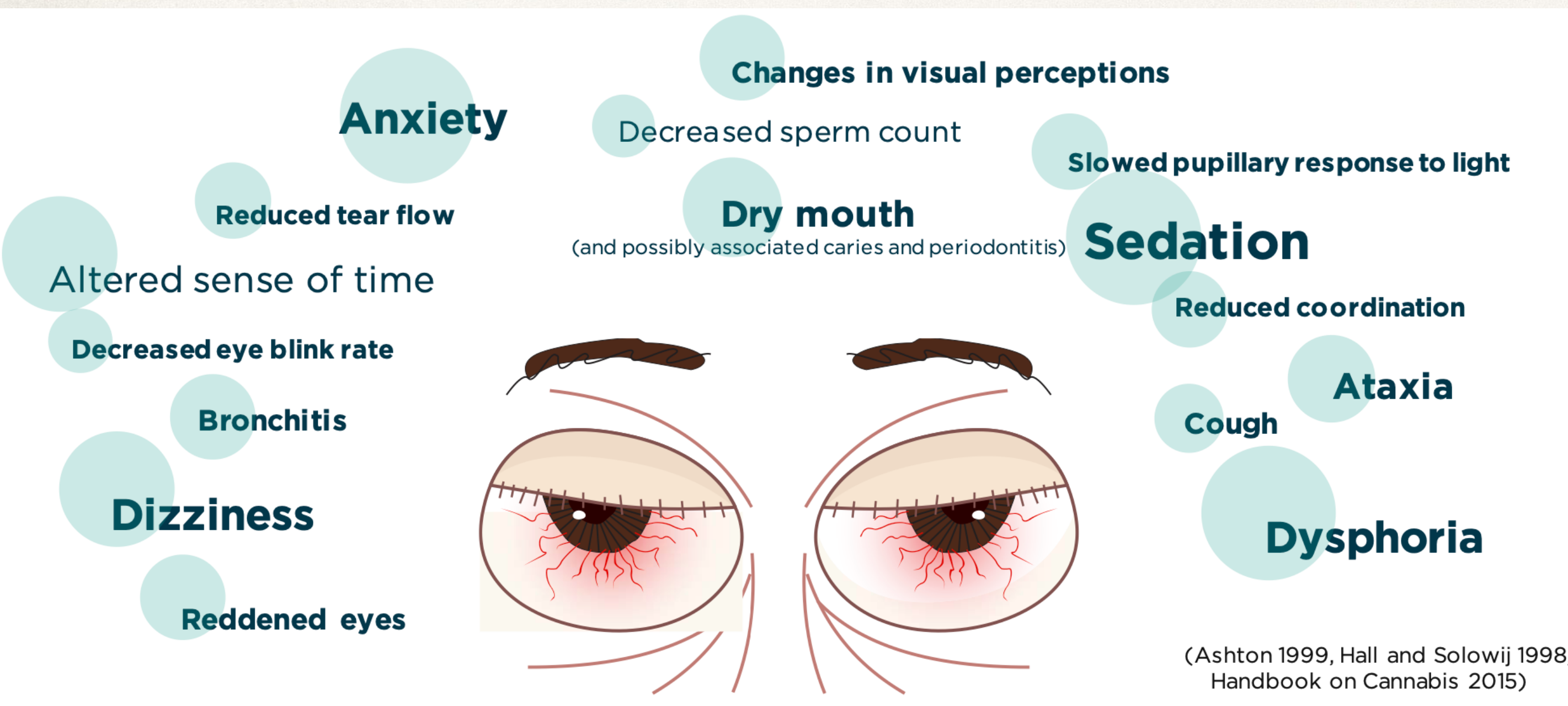
- Anxiety social disorders
- Appetite and weight loss with HIV/AIDS
- Dementia
- Parkinson's Disease
- Post Traumatic Stress Disorder (PTSD)
- Schizophrenia
- Tourette Syndrome
- Traumatic brain injury



Insufficient evidence to support or refute

- Addiction abstinence
- Amyotrophic lateral sclerosis
- Cancer
- Chorea and neuropsychiatric symptoms associated with Huntington's
- Dystonia
- Huntington's
- Irritable Bowel Syndrome (IBS)
- Parkinson's Dyskinesia

Adverse Effects/Risks



Common short-term effects of cannabis use. Size of circle depicts relative occurrence rates.

Less common and rare adverse effects:

- Hypoglycemia
- Marijuana induced psychosis (THC)
- Cannabis use disorder
- Cannabis hyperemesis syndrome

Risk factors:

- Pregnancy
- Age <25 and elderly
- Cardiovascular disease
- Family history of psychotic disorder
- Drug-Drug interactions