

PAST, PRESENT AND FUTURE OF MEDICAL CANNABIS

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HISTORICAL USE OF CANNABIS IN MEDICINE



PHARMACOLOGY OF CANNABINOIDS



ENDOCANNABINOID SYSTEM PHYSIOLOGY

The eCB system represents a microcosm of psycho-neuroimmunology or "mind-body" medicine.



SAFETY AND ADVERSE EFFECTS OF CANNABIS



IMPAIRMENTS FROM CANNABIS



FUTURE OF CANNABIS IN MEDICINE



Outline

- Medical History of Cannabis
- Pharmacology of Cannabinoids
- Endocannabinoid System Physiology
- Safety and Adverse Effects of Cannabis
- Impairments from Cannabis
- Future of Cannabis in Medicine

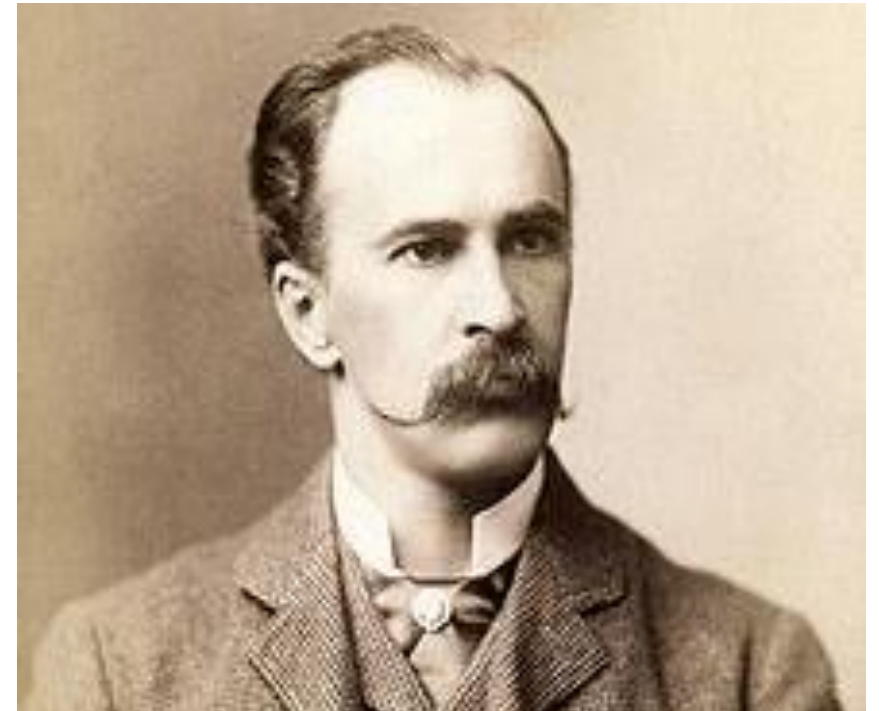


HISTORICAL USE OF CANNABIS IN MEDICINE



Historical Use of Cannabis in Medicine

- 2700 BC Emperor Shen-Nung
 - Analgesia, rheumatism, beriberi, malaria, gout and poor memory
- 1839 William O' Shaughnessy
 - Introduced medical cannabis to England
- 1854 Cannabis enters Dispensatory of US
 - Sir William Osler on migraine...“cannabis Indica is probably the most satisfactory remedy.”
- Empirical Medicine of the 19th Century
 - Combined morphine, cannabis and capsicum
 - Provided-phyto-opiod, Phytocannabinoids and phytovanilloid in one prep
 - Better outpatient pain relief than is currently available in 21st century

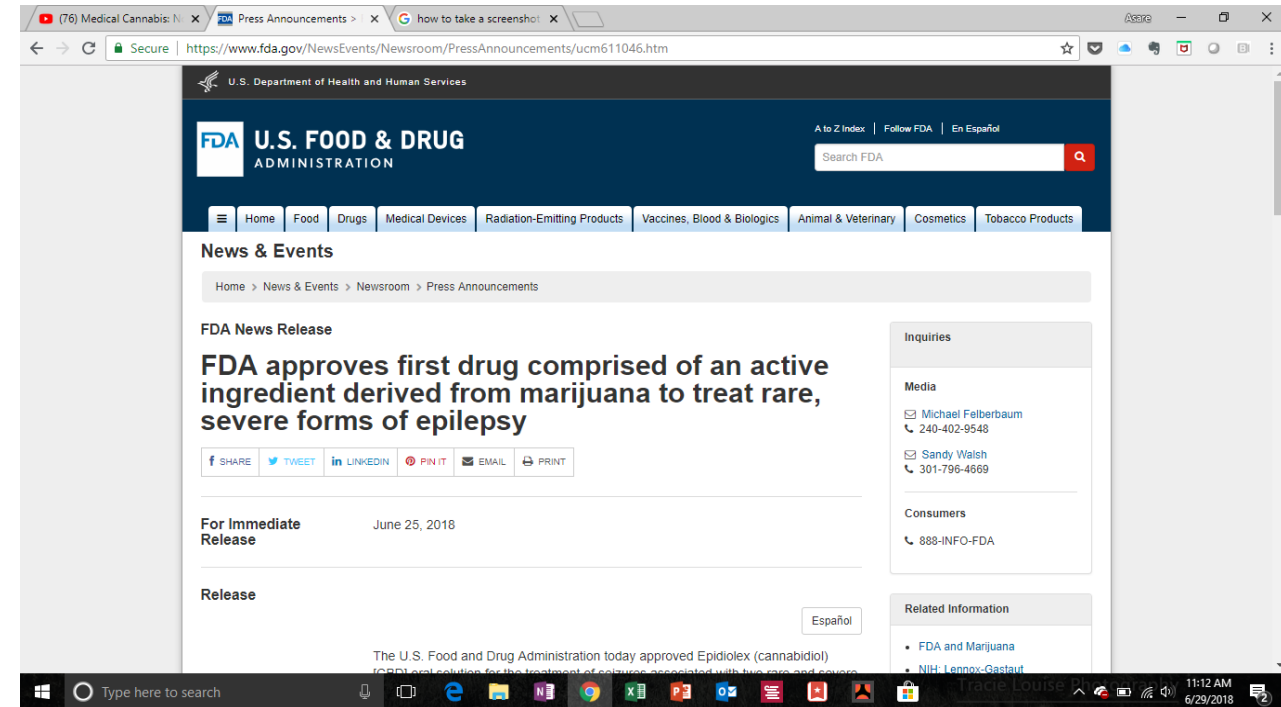


Historical Use of Cannabis in Medicine

- 19th and 20th Century
 - US Pharmacopoeia 1850-1942
 - Restrictions of sale and use 1937
 - Boggs 1951 and Narcotic Control Act of 1956 – legal penalties
- 1996 - California permits cannabis use for medicine
 - Compassionate Use Act
- 2017 - 28 states as well as Washington, DC, Guam and Puerto Rico
 - 21 states decriminalized
 - 8 states allow recreational use (AL, CA, CO, MN, MA, NV, OR, WA, DC)

Cannabis and Medicine

- Seizures, Schizophrenia, Graft vs Host Disease, NFL
- FDA approved medical cannabis since 1980
- Marinol
- Sativex: combination of CBD:THC
- Rimonabant
- Epidiolex (June 25, 2018)
- BUT cannabis remains a Schedule I drug since 1970
 - No medical benefit, high abuse potential
 - Restrict research and funding



Cannabis and Medicine History

- 1997 US National Institute of Health and British Medical Association release report on potential therapeutic effect
- 2017 Health Effect of Cannabis and Cannabinoids: Current Evidence
- 89.5% of residents and fellows felt unprepared to prescribe cannabis
- 35.3% felt ready to answer cannabis questions
- 9% of US medical schools have cannabis in their curricula
- PubMed search of “Endocannabinoid”
 - 1993: 10 citations
 - 2018: 9,032 citations

National Academies of Sciences, Engineering, and Medicine.
2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*. Washington, DC: The National Academies Press. doi:
10.17226/24625.

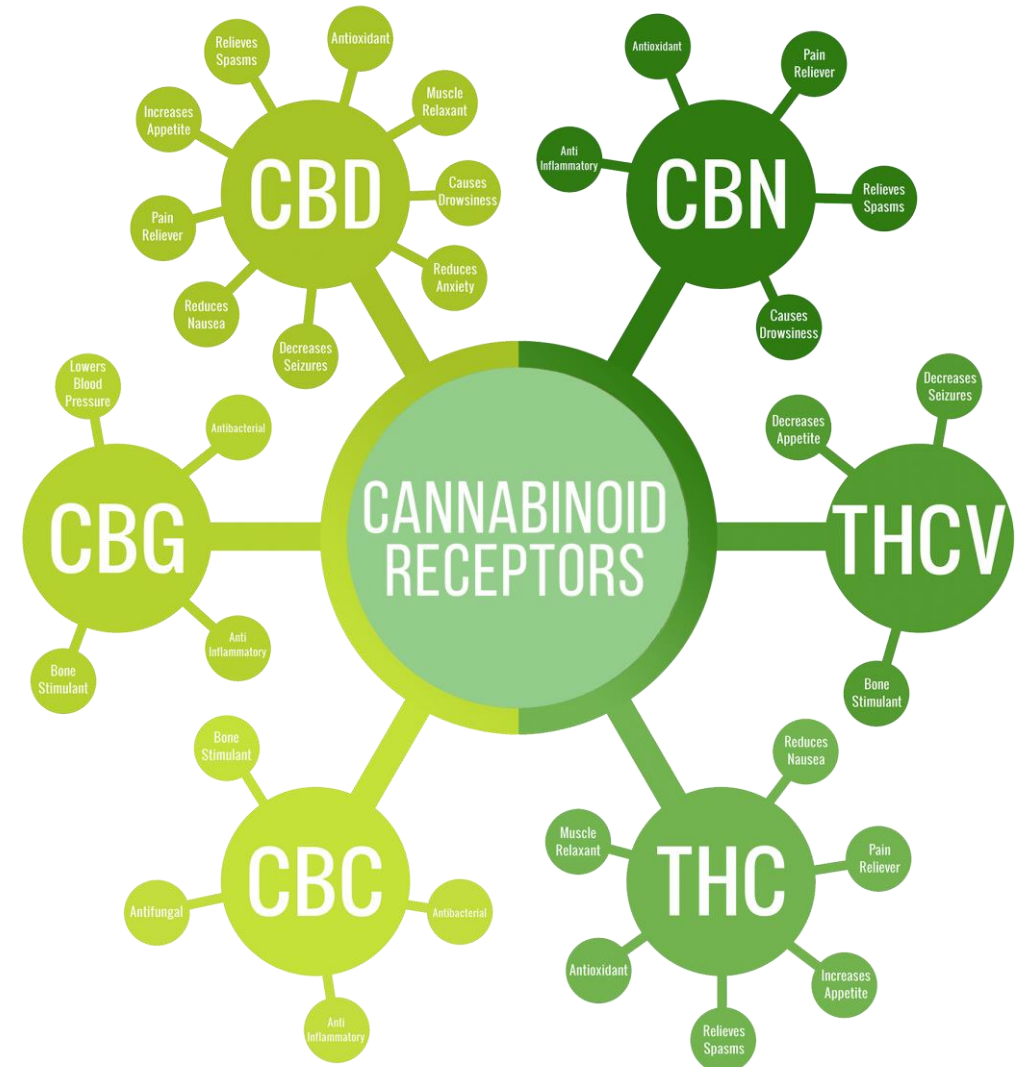


PHARMACOLOGY OF CANNABINOIDS



Cannabinoids

- Cannabinoids are compounds produced by cannabis plants which interact with the mammalian Endocannabinoid system.
- Cannabis contains more than 200 cannabinoids (THC, CBD, CBG, CBN).
- Terpenes
- Flavonoids
- Sativa vs. Indica



3 Types of Cannabinoids

01

Phytocannabinoids:
terpenophenolic 21-
C compounds found
in the genus
Cannabis(e. THC,
CBD)

02

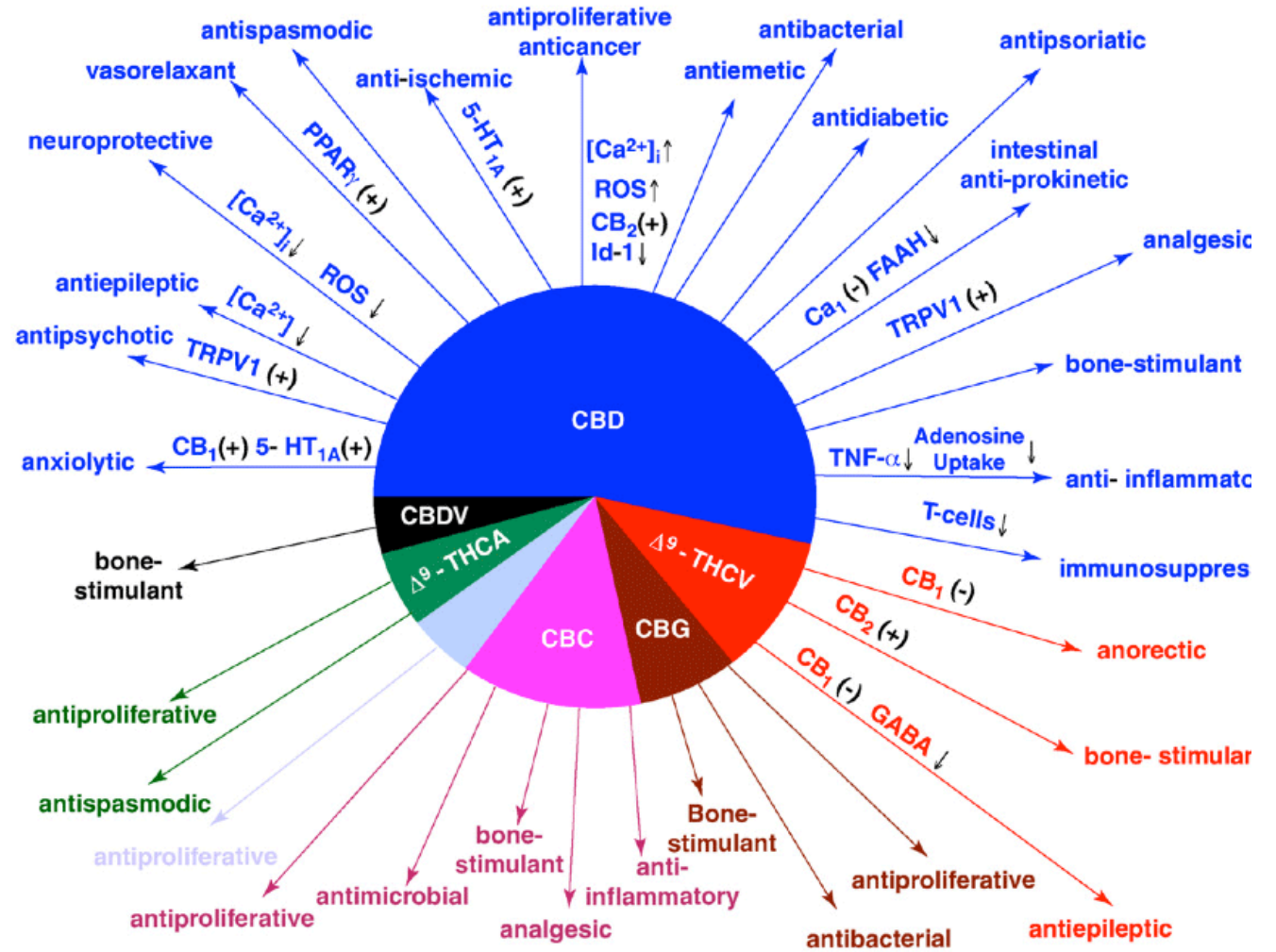
Endocannabinoids:
natural endogenous
compounds binding
cannabinoid
receptors(
anandamide and 2-
arachidonylglycerol)

03

Synthetic
cannabinoids:
Ajulemic acid
Nabilone
Dronabinol

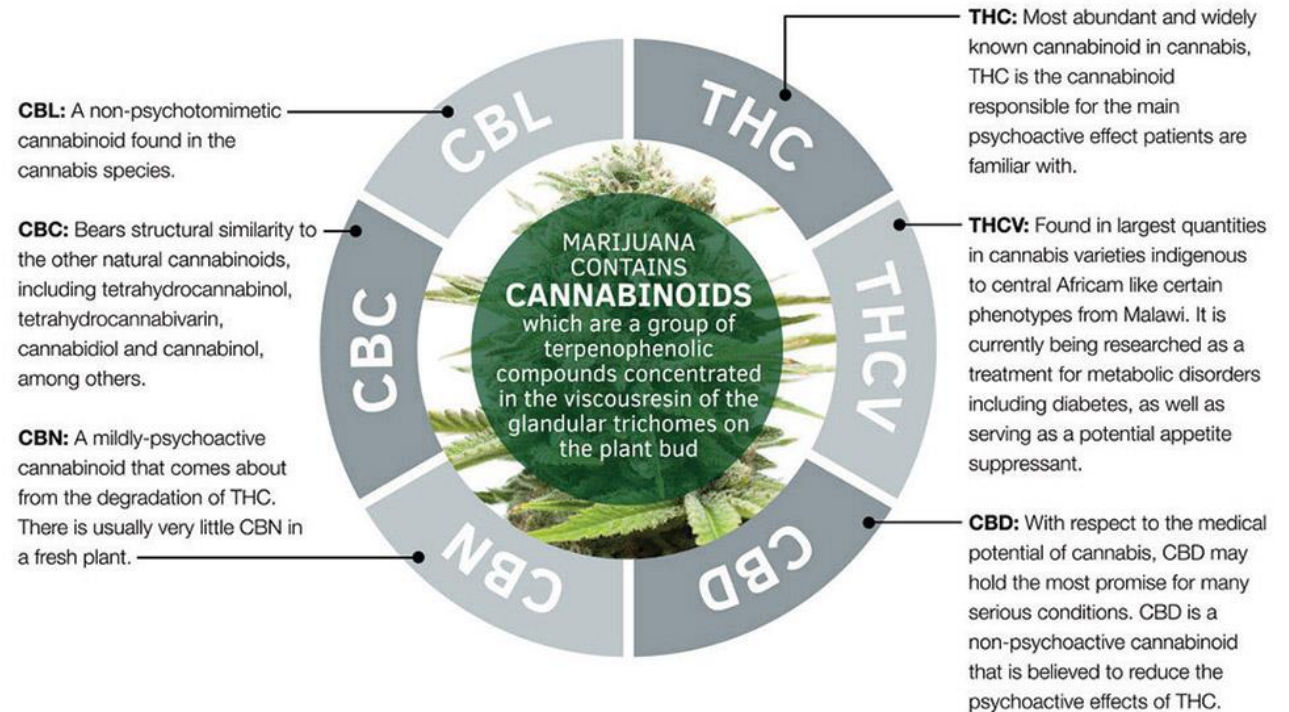
Phytocannabinoids

- Cannabis contains more than 200 cannabinoids (THC, CBD)
- Terpenes
- Flavonoids
- Sativa vs. Indica





Most Common Cannabinoids found in Cannabis


- Tetrahydrocannabinolic acid (THCA)
- Tetrahydrocannabinol (THC)
- Cannabidiolic Acid (CBDA)
- Cannabidiol (CBD)
- Cannabigerol (CBG)
- Cannabichromene (CBC)
- Tetrahydrocannabivarin (THCV)



The Entourage Effect: Phytocannabinoids and Terpenes

- Naturally occurring aromatic oils that produce different sensations and effects on the body.
- Terpenes share precursor molecule with Phytocannabinoids, flavors and fragrances.
- Cannabis-derived terpenes include:
 - Limonen, Myrcene, a-pinene, linalool, B-caryophyllene, caryophyllene oxide, nerolidol and phytol


COMMON CANNABIS TERPENES


	LIMONENE	PINENE	MYRCENE	LINALOOL	CARYOPHYLLENE
	CITRUS, LEMON	PINE	MUSKY, EARTHY	FLORAL, SWEET	WOOD, SPICE
AROMA					
	STRESS RELIEF, ELEVATED MOOD	CREATIVITY, ALERTNESS, EUPHORIA	SEDATION, BODY HIGH, RELAXATION	CALMING, RELAXATION	NO NOTED EFFECTS
EFFECTS					
	ANTI-ANXIETY, ANTIDEPRESSANT	ASTHMA, ANTIFLAMMATION	ANTIOXIDANT, INSOMNIA	ANTI-ANXIETY, SEDATING	CHRONIC PAIN, INSOMNIA
MEDICAL BENEFITS					
	SUPER LEMON HAZE, LEMON SKUNK	TRAINWRECK, BUBBA KUSH	WHITE WIDOW, BLUE DREAM	SKYWALKER OG, HEADBAND	WHITE WIDOW, OG KUSH
STRAINS					
	CITRUS PEPPERMINT	PINE, PARSLEY, BASIL, ROSEMARY	MANGO, THYME, LEMONGRASS	LAVENDER, ROSEWOOD	PEPPER, CLOVE
ALSO FOUND IN					

ENDOCANNABINOID SYSTEM PHYSIOLOGY

The eCB system represents a microcosm of psycho-neuroimmunology or “mind-body” medicine.



Cannabinoids and Health Conditions

ADD/ADHD

ALS

Alzheimer's

Anorexia

Anxiety

Asthma

Ataxia

Bipolar

Cachexia

Cancer

Chronic fatigue

Chronic pain

Cramps

Crohn's

Diabetes

Depression

Epilepsy

Fever

Fibromyalgia

Glaucoma

Hepatitis

HIV/AIDS

Incontinence

Insomnia

Migraine

MRSA

Multiple Sclerosis

Nausea

Neuralgia

Neuropathy

Parkinson's

PMS

PTSD

Rheumatoid Arthritis

Seizure disorders

Sickle cell anemia

Spasms

Spinal injury

Stroke

Tourette's

Vomiting

- Why is one plant involved in so many disease processes?
- The eCB system represents a microcosm of psycho-neuroimmunology or “mind–body” medicine.

NEUROSCIENCE

Stout Guards of the Central Nervous System
R. Mechoulam and A. H. Lichtman

www.sciencemag.org SCIENCE VOL 302 3 OCTOBER 2003

BJP British Journal of Pharmacology

Themed Issue: Cannabinoids in Biology and Medicine, Part I

REVIEW

Endocannabinoids and traumatic brain injury
Esther Shohami, Ayelet Cohen-Yeshurun, Lital Magid, Merav Algali and Raphael Mechoulam

Endocannabinoid signaling as a synaptic circuit breaker in neurological disease
István Katona & Tamás F Freund
Nature Medicine, Sept 2008, pp923 - 930

J Neuroimmune Pharmacol (2015) 10:268–280
DOI 10.1007/s11483-015-9584-2

INVITED REVIEW

Cannabinoid Signaling and Neuroinflammatory Diseases: A Melting pot for the Regulation of Brain Immune Responses
Valerio Churchillù • Alessandro Leuti • Mauro Maccarrone



US006630507B1

(12) **United States Patent**
Hampson et al.

(10) **Patent No.:** **US 6,630,507 B1**

(45) **Date of Patent:** **Oct. 7, 2003**

(54) **CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS**

(75) **Inventors:** Aidan J. Hampson, Irvine, CA (US); Julius Axelrod, Rockville, MD (US); Maurizio Grimaldi, Bethesda, MD (US)

(73) **Assignee:** The United States of America as represented by the Department of Health and Human Services, Washington, DC (US)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) **Appl. No.:** **09/674,028**

(22) **PCT Filed:** **Apr. 21, 1999**

OTHER PUBLICATIONS

Windholz et al., The Merck Index, Tenth Edition (1983) p. 241, abstract No. 1723.*

Mechoulam et al., "A Total Synthesis of $\text{d1-}\Delta^1\text{-Tetrahydrocannabinol}$, the Active Constituent of Hashish¹," *Journal of the American Chemical Society*, 87:14:3273-3275 (1965).

Mechoulam et al., "Chemical Basis of Hashish Activity," *Science*, 18:611-612 (1970).

Ottersen et al., "The Crystal and Molecular Structure of Cannabidiol," *Acta Chem. Scand. B* 31, 9:807-812 (1977).

Cunha et al., "Chronic Administration of Cannabidiol to Healthy Volunteers and Epileptic Patients¹," *Pharmacology*, 21:175-185 (1980).

Constroe et al., "Acute and Chronic Antiepileptic Drug Effects in Audiogenic Seizure-Susceptible Rats," *Experimental Neurology*, Academic Press Inc., 70:626-637 (1980).

Turkanis et al., "Electrophysiologic Properties of the Cannabinoids," *J. Clin. Pharmacol.*, 21:449S-463S (1981).

- Anandamide and 2-AG are produced by the nervous system upon both chemical and mechanical trauma (Mechoulam, 2002).
- Delta-9-THC, CBD, AEA, 2-AG, HU-220 all decrease glutamate excitotoxicity(Baker, 2003)
 - Reduce seizure activity
 - Limit infarct size post-stroke
- Cannabinoids effective at reducing and preventing perinatal brain injury

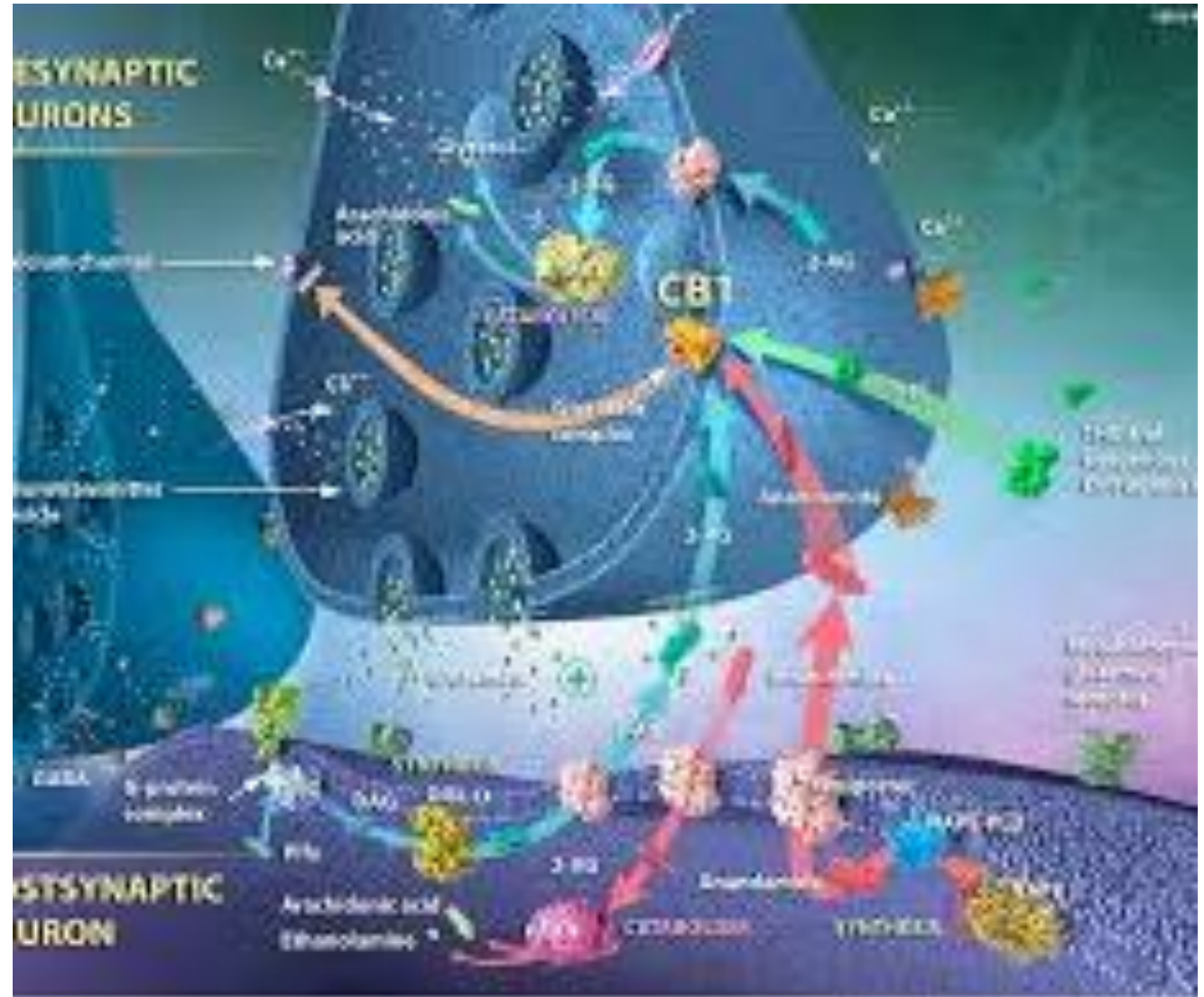
Neural Protection: Federal Patent

Endocannabinoid System (ECS)

ECS: internal homeostatic regulatory systems with 3 components:

1. Endocannabinoids
2. CB1, CB2, TRPV1 receptors
3. Regulatory enzymes (Fatty Acid Amide Hydrolase, Monacyl glycerol)

Endocannabinoids are produced on demand, retrograde travel to presynaptic neurons, inhibiting neurotransmitter release.

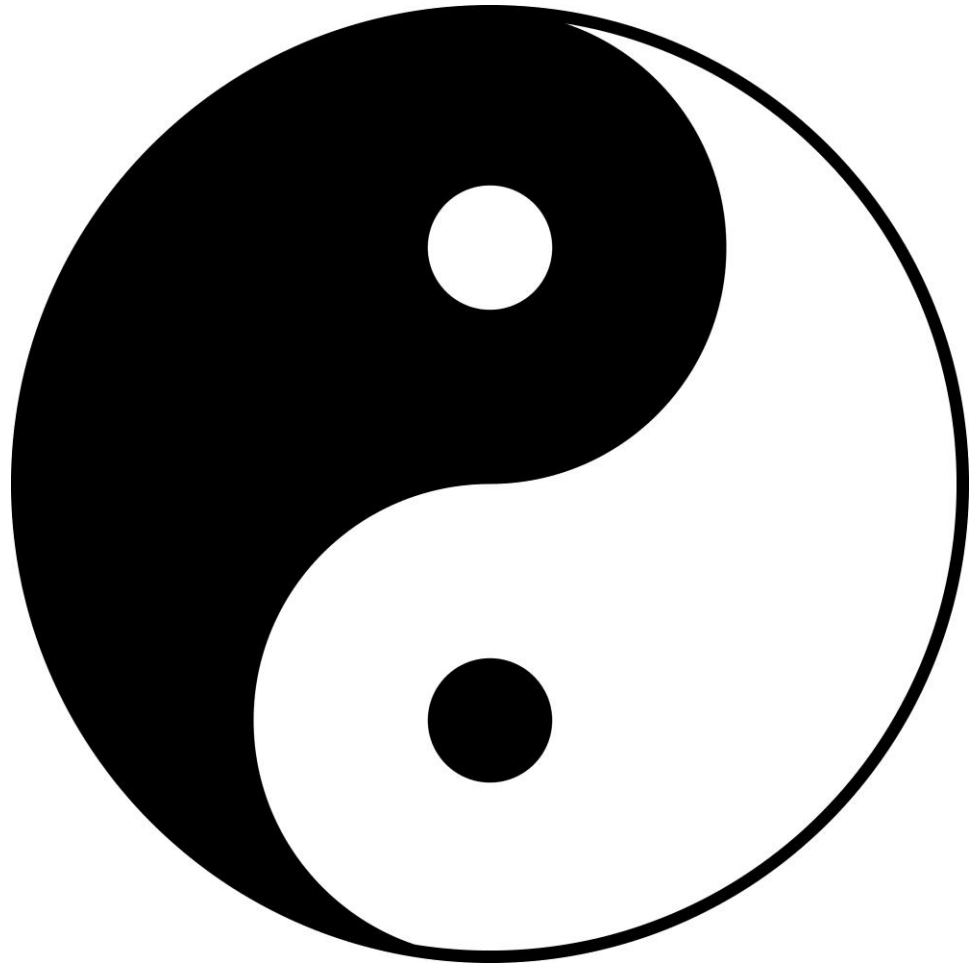


CB1 Receptor

- CB1: most abundant G-protein-coupled receptor in the brain with major neuromodulatory function
- CB1 receptors are present in areas of nociception (pain modulation)
- Cerebellum, limbic system, basal ganglia and reward pathways, substantia nigra and periaqueductal grey matter
 - Movement, addiction, sex and food
- Limited distribution in brainstem and not found in the Medullary respiratory centers
 - Inherent safety mechanisms
- CB1 also found in testis, presynaptically on sympathetic nerve terminals, adrenal glands, heart, lungs, prostate, bone marrow, thymus and tonsils

CB2 Receptors

- CB2 impacts pain modulations and plays an important role in immune function and inflammation.
- CB2 activation reduces nociception in a variety of models
 - Tactile, thermal, allodynia, mechanical and thermal hyperalgiias and writhing
- Neuropathic modulation in pain thought to be related to CB2 receptors on microglia and reducing cytokine-mediated neuroinflammation



Endocannabinoid System Function

- Endocannabinoid System: 500 millions years old
 - Very primitive system just like endogenous opioid system
- Mood, stress response, pain, embryology, memory, sleep, immune response, reproductive function, energy metabolism
- Preserved across all vertebrate
- Homeostasis: maintenance of dynamic balance

SAFETY AND ADVERSE EFFECTS OF CANNABIS



Safety of Cannabinoids

Cannabinoids have a high therapeutic index.

No fatalities reported directly related to the toxicity of any cannabinoid, even at extremely high doses.

Potential severe cognitive, psychomotomimetic and substance abuse-related adverse effects due to THC in the young or cannabis-naïve.

Side Effects of Cannabis

- Dizziness
 - Dry mouth
 - Nausea
 - Fatigue
 - Sleepiness
 - Euphoria
 - Depression
 - Vomiting
- Impaired balance
 - Paranoia
 - Confusion
 - Anxiety
 - Disorientation

Risk of Dependency with Use of Illicit Drugs

Lifetime risk of dependency

- Cannabis 5%
- Stimulants 11%
- Alcohol 15%
- Nicotine 32%
- Heroin 23%
- Cocaine 17%

Highest risk of dependency

- Poor academic achievement
- Deviant behavior in childhood
- Poor parental relationship
- Parental history of drug abuse



IMPAIRMENTS FROM CANNABIS



Impairment is Real with Cannabis

- Can cannabis cause temporary changes in performance?
 - Short term changes in psychomotor performance are exacerbated when cannabis is consumed in combination with alcohol.
 - Route of administration will also impact drug effects.
 - Oral THC is associated with delayed onset and prolonged duration of drug effect, greater drug bioavailability and greater THC to 11-hydroxy THC conversion.
 - Habitual consumers may become tolerant to drug effect over time (Marinol, Sativex).



Drug Testing and Impairment

- Standard drug detection methods do not identify impairment of performance
 - (presence of THC, 11 hydroxy THC, and or carboxy THC)
- Residual traces of THC may be present in blood, particular in habitual users, well beyond any expected period of drug induce impairment
- Blood levels THC does not correct with IMPAIRMENTS
 - Influence on behavior diminishes relatively rapidly some 60 minutes (*National Highway Traffic Safety Administration, 2003*) to 2.5 hours (*Sewell et al., 2009*) after inhalation.



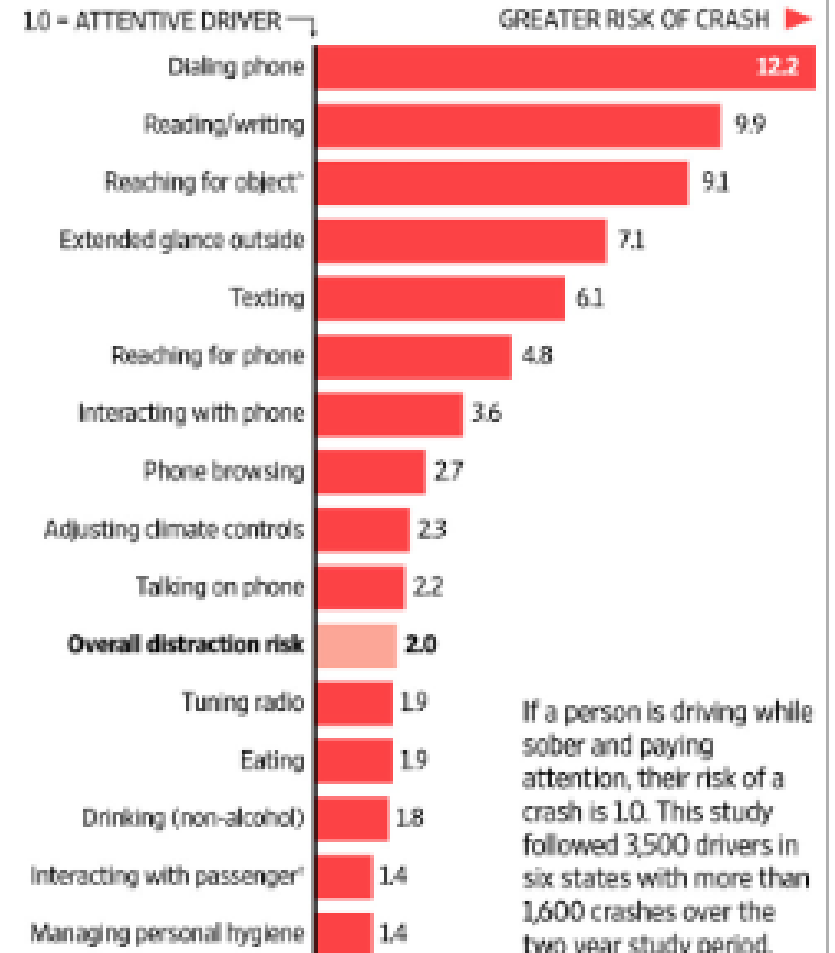
Cannabis and Driving

- Cannabis is generally associated with less elevated risk of accidents compared to other drugs.
 - THC positive drivers OR 1.3 following adjustment
 - “THC’s adverse effects on driving performance appear relatively small.” (NHTSA. 1993. *Marijuana and Actual Driving Performance: Final Report*)

Eyes Off The Road

A Virginia Tech study found that driver distraction is a significant cause of accidents. New technologies are adding ways to distract people, and also giving companies new ways to keep them focused on the road.

Risk of a crash caused by type of distraction



*Other than phone †Teen/adult

If a person is driving while sober and paying attention, their risk of a crash is 1.0. This study followed 3,500 drivers in six states with more than 1,600 crashes over the two year study period.

Cannabis As an Exit Drug

- 350 individuals surveyed at medical cannabis dispensary
 - 40% use as substitute for alcohol
 - 26% use as substitute for illicit drugs
 - 66% use as substitute for prescription drugs
- Most common reasons for substituting
 - Less adverse side effects (65%), better symptom management (57%), decreased withdrawal potential with cannabis (34%)



FUTURE OF CANNABIS IN MEDICINE



Future of Cannabinoid Medicine

Endocannabinoid signaling involved in multiple disease process

Clinical Endocannabinoid Deficiency

Opioid Sparing Properties

CB2 Mediated Pharmacology

Phyto-combination Drugs Developed

Recreational Use

Public Health Implications

Schedule 1 Status



THANKS FOR YOUR ATTENTION

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