

Literature Review on the  
History and Therapeutic Implications of  
Cannabis  
in Traditional Chinese Medicine

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# Outline

- ◆ Introduction
- ◆ Definitions
- ◆ Thesis Introduction
- ◆ Endocannabinoid System
- ◆ History and Benefits of Cannabis
- ◆ Chinese Medicine and the ECS
- ◆ Thesis Conclusion



# Introduction

- ◆ Why did I look into Cannabis sativa L. for my patients, family and myself?
- ◆ Why did I do my Capstone for my Doctorate on the History and Medical Benefits of Cannabis?



# Definitions

- ◆ Cannabinoid = any of the chemical compounds that are the active principles of cannabis.
- ◆ Endocannabinoid System = The ECS is an elegant, lock-and-key like, cell signaling, receptor-site system that may be activated by endocannabinoids produced naturally in your body, or by phytocannabinoids (plant-based cannabinoids) that mimic those produced in your body.
- ◆ Receptor = These cannabinoids fit lock & key to receptor sites (CB1 and CB2 receptors that are located ALL over the body) and may release an intricate cascade of neurotransmitters that communicate vital information to cells, tissues, organs and glands critical to maintaining optimal health and homeostasis.



# Health Conditions Influenced by Cannabinoids

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

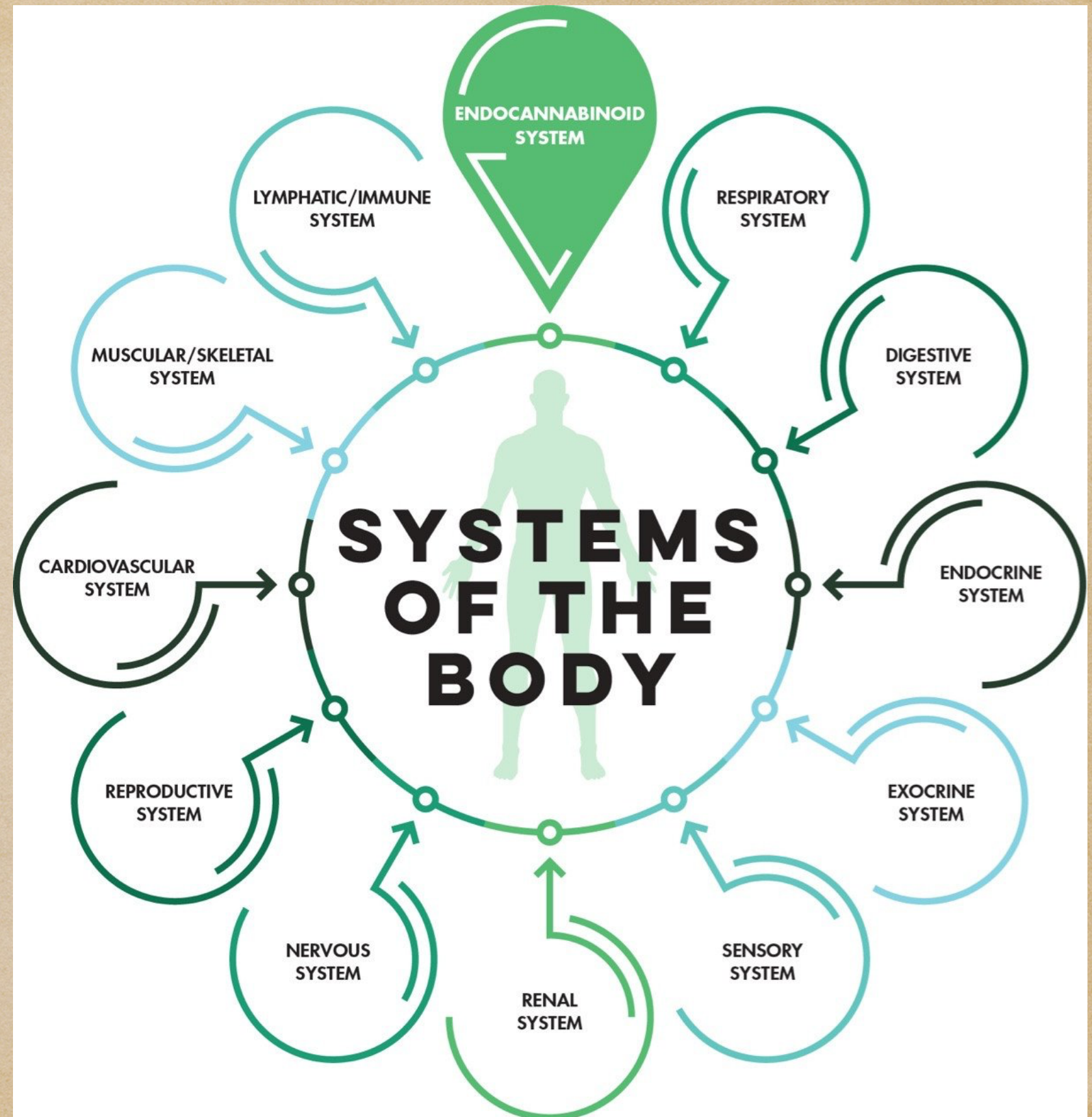
Tourette's

Vomiting



Why does  
one herb  
help so  
many  
different  
conditions?

The  
Endocannabinoid  
System

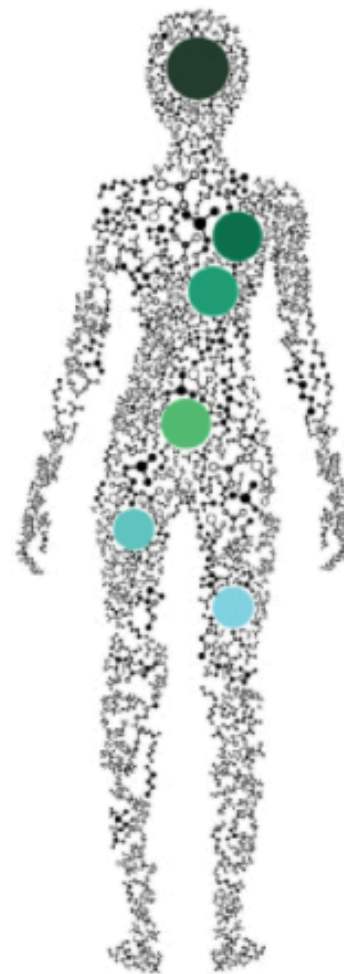




YOUR ENDOCANNABINOID SYSTEM IS INVOLVED  
IN EVERY ASPECT OF HUMAN HEALTH

THE ENDOCANNABINOID SYSTEM MEDIATES SYSTEMIC HEALTH

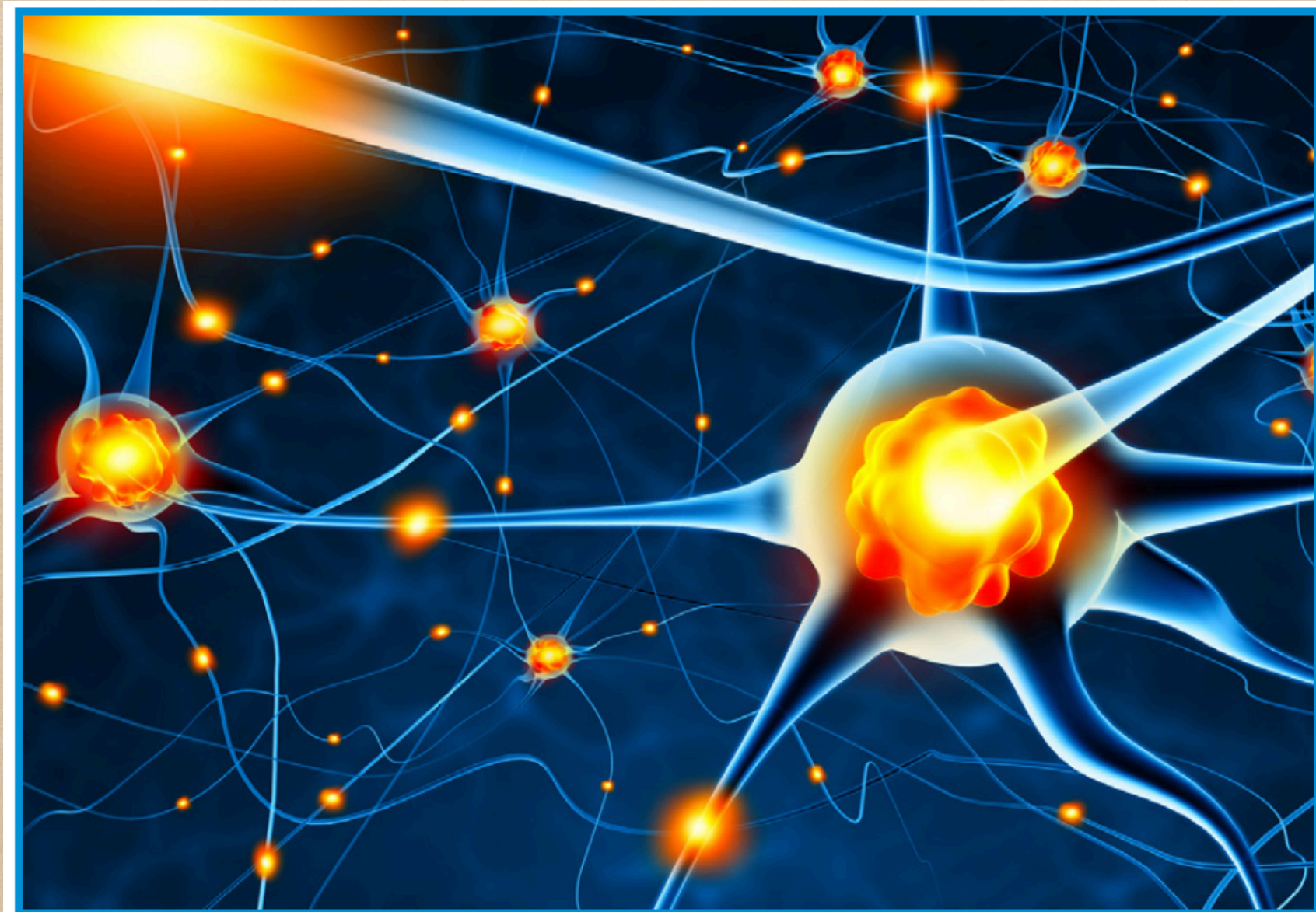
LIVER  
BRAIN  
HEART  
SPLEEN  
LYMPH CELLS  
BLOOD VESSELS  
NERVOUS SYSTEM  
FAT AND ADIPOSITY



LUNG  
BONE  
KIDNEY  
MUSCLE  
BLOOD CELLS  
IMMUNE SYSTEM  
DIGESTIVE SYSTEM  
ENDOCRINE GLANDS



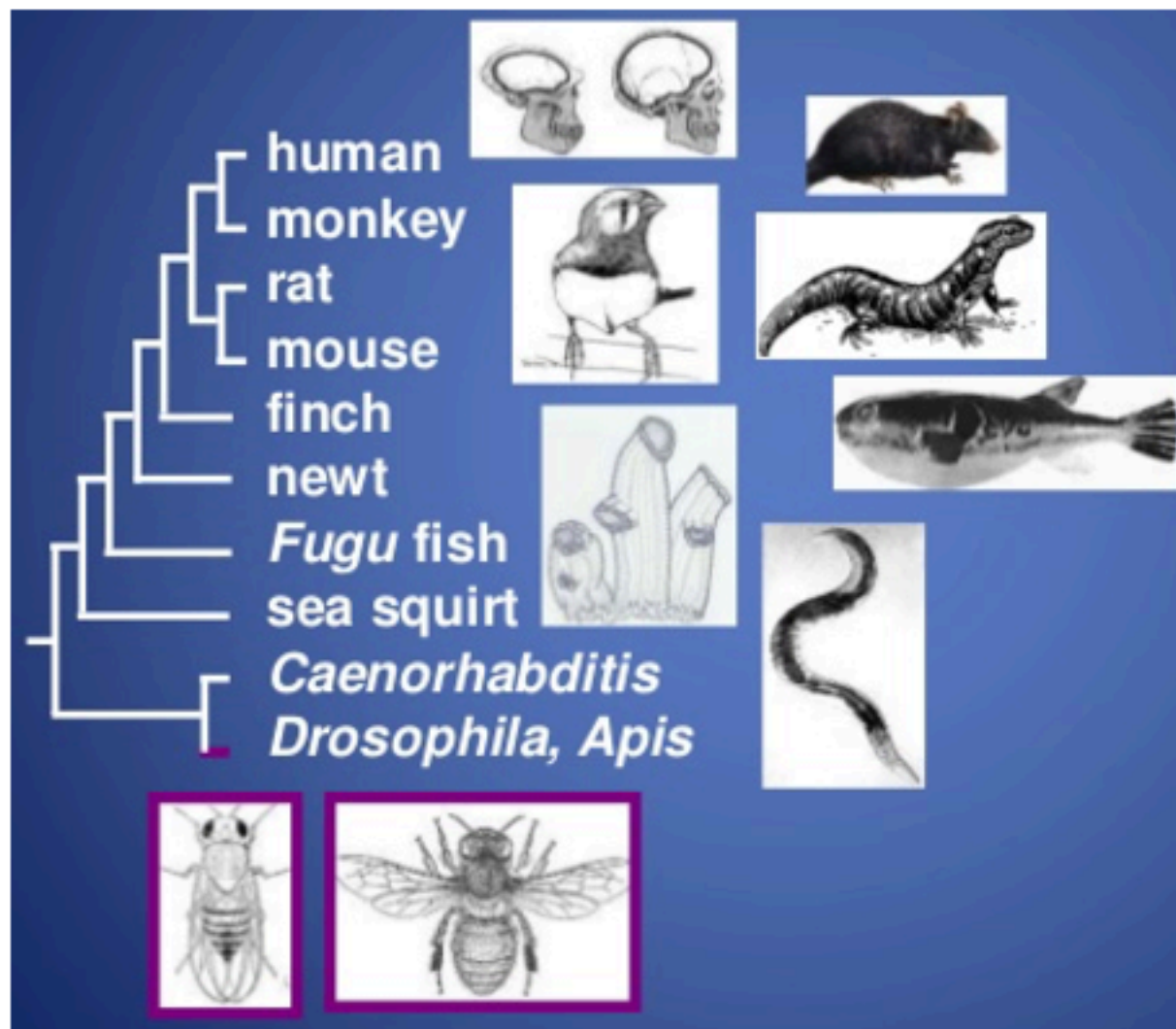
The ECS is believed to have more cellular receptor sites than any other receptor system.





# Cannabinoid Receptors

## CB Receptors Evolved 600 Million Years Ago



Genomic and phylogenetic studies indicate that CB receptors evolved around 600 million years ago.

CB receptors are present in every vertebrate investigated to date.

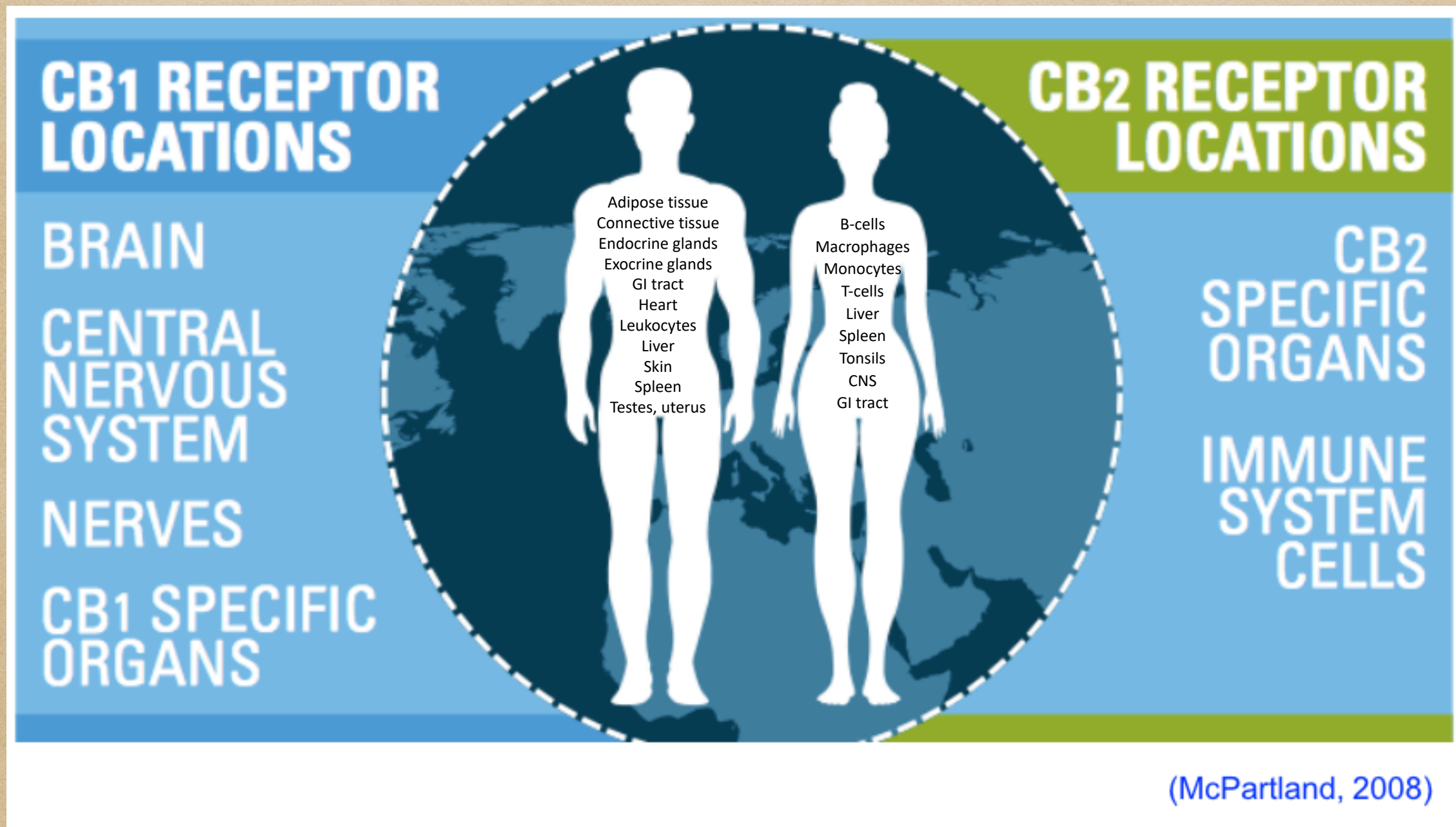
CB receptors are absent in non-chordate invertebrates (insects, nematodes, Hydra), fungi, and plants.

CB receptors existed long before cannabis evolved, ca 25 million years ago.

(McPartland et al 2001, Matias et al 2005 McPartland et al 2007)



# Cannabinoid Receptors





# Endocannabinoid System Modulates:

- Embryonic Development
- Neural Plasticity
- Neuroprotection
- Immunity
- Inflammation
- Apoptosis
- Carcinogenesis
- Pain and emotional memory
- Hunger
- Metabolism



# Cannabinoids

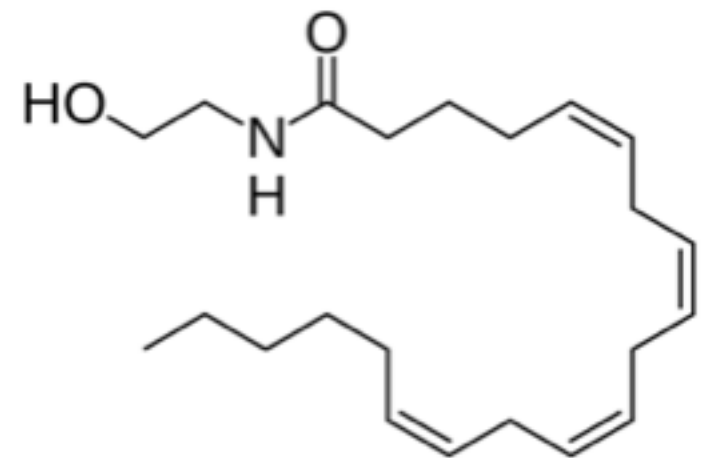
1. Phytocannabinoids occur in plants, such as Cannabis
2. Endocannabinoids occur naturally in the brain
3. Synthetic cannabinoids are created in laboratories and are not known to exist naturally
4. Cannabimimetic terpenes such as Coneflower (Echinacea), Black Pepper (hu jiao), Rosemary (mi die xiang), Black Truffles (Tuber melonsporium), Carrot, Chinese Rhododendron (man shan hong), Helichrysum, Flax (ya ma zi), Frankincense (ru xiang), Liverwort, Kava kava, Maca



# Cannabinoids - Endogenous

## **Anandamide (AEA)**

- Ananda is Sanskrit for Bliss
- CB1 and CB2 agonist
- The first endogenous cannabinoid identified - 1982 by W.A. DeVane in Raphael Mechoulam's group at Hebrew University, Israel.
- Anandamide also found in chocolate
- Produced by body during meditation
- Part of "Runners High" effect Here

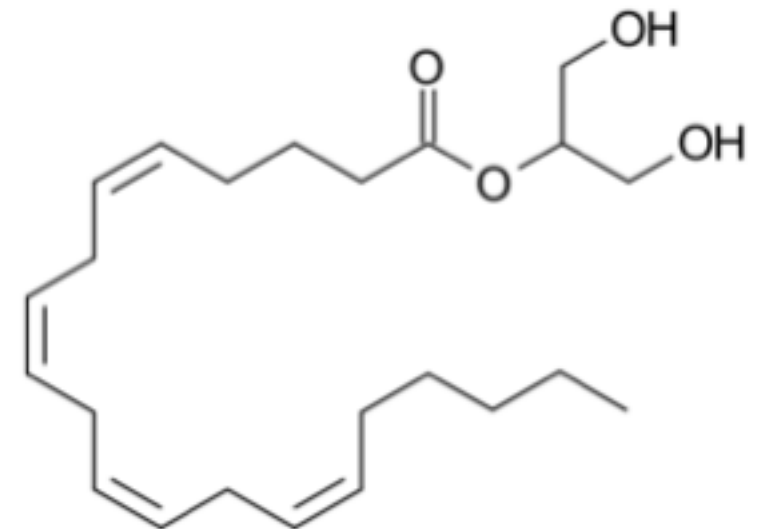




# Cannabinoids - Endogenous

## 2-Arachidonoylglycerol (2-AG)

- High levels in CNS (much greater than Anandamide)
- Neuromodulator
- 2-arachidonoylglycerol (2-AG) made from Omega-6 fatty acids
- 2nd most common endocannabinoid - CB1 and CB2 agonist
- 2-AG also found in animal milk, including breast milk
- Anandamide is a neurotransmitter - chemical signaling messenger across neural synapses
- Has a cell membrane transporter system

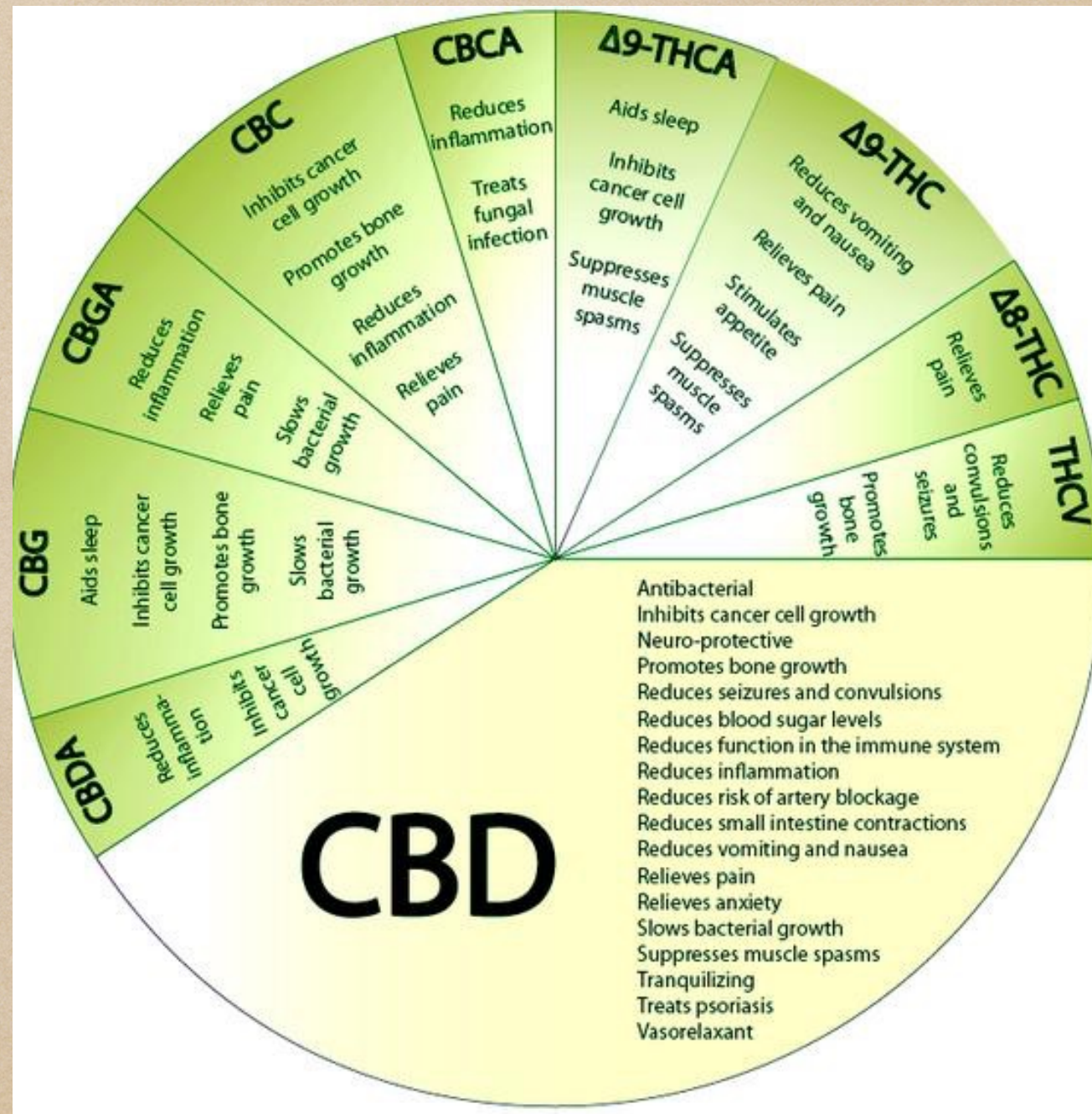


Gonsiorek, W., Lunn, C., Fan, X., Narula, S., Lundell, D., & Hipkin, R. W. (2000). Endocannabinoid 2-arachidonyl glycerol is a full agonist through human type 2 cannabinoid receptor: antagonism by anandamide. *Molecular Pharmacology*, 57(5), 1045-1050.



# Cannabinoids - Exogenous

- THC - Psychoactive
- CBD - Non-Psychoactive
- 150+ types of cannabinoids





# Cannabinoids - Exogenous

[illegible]



# Cannabinoid Pharmacology Milestones

- 1964  $\Delta^9$ -THC synthesized and structure identified
- 1980s Synthetic cannabinoids
- 1988 **CB1 receptor identified**
- 1990 CB1 receptor cloned
- 1992 **CB2 receptor**
- 1992 **Anandamide**
- 1993 CB2 receptor cloned
- 1995 **2-arachidonylglycerol (2AG) identified**
- 1994-7 Receptor antagonists
- 1998 Endogenous ligands shown to be analgesic
- 2001 Noladin ether identified
- 2000+ Synthetic cannabinoids, more on the endogenous system, biosynthesis and degradation, delivery systems.

Howlett, A. C., Barth, F., Bonner, T. I., Cabral, G., Casellas, P., Devane, W. A., ... Pertwee, R. G. (2002). International Union of Pharmacology. XXVII. Classification of Cannabinoid Receptors. *Pharmacological Reviews*, 54(2), 161.



# Endocannabinoid System Review

- Inside all vertebrates
- Main function: homeostasis
- System of receptors and agonists
- Regulates "relax, eat, sleep, forget, and protect"
- A "microcosm of psychoneuroimmunology, or mind-body medicine"



# Cannabis Plant

Kingdom Plantae - Plants

Subkingdom Tracheobionta - Vascular plants

Superdivision Spermatophyta - Seed plants

Division Magnoliophyta - Flowering plants

Class Magnoliopsida - Dicotyledons

Subclass Hamamelididae

Order Urticales

Family Cannabaceae - Hemp family

Genus Cannabis L. - hemp

Genus Humulus L. - hop

HEMP

Species Cannabis sativa L. - marijuana

Subspecies Cannabis sativa L. ssp. indica (Lam.) E. Small & Cronquist - marijuana

Subspecies Cannabis sativa L. ssp. sativa - marijuana

Variety Cannabis sativa L. ssp. sativa var. sativa - marijuana

Variety Cannabis sativa L. ssp. sativa var. spontanea Vavilov - marijuana



**Sativa**  
taller plant and skinner leaves



**Indica**  
bushier plant and wider leaves



# Therapeutic Effects of Cannabis and Cannabinoids - Literature Review

- ◆ Neurological and movement disorders: antispasmodic, epilepsy
- ◆ Cancer: chemotherapy-induced nausea/vomiting, anti-angiogenesis, pain
- ◆ Addiction and abuse potential, safety
- ◆ Pain

National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington (DC): National Academies Press (US); 2017 Jan 12. 4, Therapeutic Effects of Cannabis and Cannabinoids. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK425767/>



# Timeline of Key Discoveries

8000 BCE existing evidence suggests that there was Cannabis use in Europe and East Asia started in the early Holocene

2737 BCE Shen Nung prescribed Cannabis tea for gout, rheumatism, malaria and poor memory

2698-2205 BCE The Yellow Emperor Huangdi wrote the Neijing, which outlines cannabis for certain ailments

1AD Shennong Bencao Jing detailed uses for cannabis in Chinese medicine

140-208AD Hua Tuo is first medical practitioner to use cannabis with acupuncture for anesthesia for surgery

1840 William B. O'Shaughnessy, an Irish physician working at the Medical College and Hospital in Calcutta, first introduced cannabis (Indian hemp) to Western medicine as a treatment for tetanus and other convulsive diseases

1845 French physician Jean-Jacques Moreau de Tours experimented with the use of cannabis preparations for the treatment of mental disorders

1851 Cannabis was included in the 3rd edition of the *Pharmacopoeia of the United States*

1937 Marihuana Tax Act

1942 The American Medical Association removed cannabis from the 12th edition of *U.S. Pharmacopeia*

*The Controlled Substance Act of 1970*

2008 Worlds oldest stash of psychoactive cannabis was found in the 700AD tomb of a shaman in remote China



# Today

- ◆ To date, 28 states & D.C. have legalized cannabis for medical conditions. 8 of these states and D.C have also legalized cannabis for recreational use.
- ◆ 55 Million Americans reported using Cannabis during 2017 (tobacco 36.5m)



# Cannabis in Chinese Medicine

Character: Chinese Simplified  
Pronunciation: Hanyu Pinyin  
(Mandarin = Standard Chinese)

大麻

dà má

HUO MA REN



flower (hua)    skin (pi)  
root (gen)    male seed (fen)  
leaf (ye)    seed (ren)



The Yellow Emperor, Huang Ti



Portrait of the Red Emperor Shen Nung



Brand, E. J., & Zhao, Z. (2017). Cannabis in Chinese Medicine: Are Some Traditional Indications Referenced in Ancient Literature Related to Cannabinoids? *Frontiers in Pharmacology*, 8, 108. <https://doi.org/10.3389/fphar.2017.00108>



# Chinese Medicine and the ECS

Huang Di Nei Jing Su Wen first question when the Emperor asked Qi Bo how the ancient people lived to exceed 100 years without weakening: the ancients lived a healthy lifestyle. "they modeled [their behavior] on yin and yang"; eating and drinking was moderate; rising and resting had regularity; and they were able to keep physical form and shen together.

In this same section, Qi Bo says the sages taught that "quiet peacefulness, absolute emptiness, the true qi follows (these states), When jing and shen are guarded internally, where could a disease come from?



# Chinese Medicine and the ECS

Chapter 13 of the Huang Di Nei Jing Su Wen 'Discourse on Moving the Essence and Changing the Qi'

- Huang Di asked: "I have heard that, when [the people] in antiquity treated a disease, they simply moved the essence and changed the qi. They were able to invoke the origin and [any disease] came to an end.
- They moved and transformed the body's Jing qi without herbs or needles, much less medications or surgeries to maintain balanced health.

Chapter 5, Section 2 of the Huang Di Nei Jing Su Wen

- Beautifully shows how Jing, Qi and Shen move between the exogenous and endogenous



# Chinese Medicine and the ECS

## Chapter 3 of the Neijing Suwen, Section 1.4

- "Hence, when the sages concentrated essence and spirit and when they ingested the qi of heaven they communicated with the spirit brilliance."
- "If one misses the [sequence of the seasons], then internally the nine orifices are closed, and externally muscles and flesh are congested. The guard qi dissipates. This is called self injury; it is the deletion of qi."



# Chinese Medicine and the ECS

## Chapter 3 of the Neijing Suwen: 'Discourse on How the Generative Qi Communicates with Heaven'

- "If the spirit is at peace, the heart is in harmony; when the heart is in harmony, the body is whole; if the spirit becomes aggravated the heart wavers, and when the heart wavers the body becomes injured; if one seeks to heal the physical body, therefore, one needs to regulate the spirit first."
- Pathogens cannot invite and cause damage when jing, qi and shen are present and strong, even if nature's cycles are disrupted or plagues are present. Thus, under homeostatic conditions, these endogenous vital substances adequately nourish and tonify organs and channels.



# Chinese Medicine benefits the ECS

Qi Gong

Acupuncture

Herbal Medicine

Electro-Acupuncture

Food as Medicine

## Clinical Endocannabinoid Deficiency Syndrome

Dr. Ethan Russo, University of Pennsylvania



# Endocannabinoid Deficiency

A lack of endocannabinoid tone is thought to be present in conditions of poor diet, lack of exercise, drug abuse, environmental toxins, genetic factors, and chronic stress and compromised health. This, in turn, may have adverse consequences on a plethora of physiological processes. The term for this condition is "Clinical Endocannabinoid Deficiency Syndrome" (CEDS).

Supporting scientific evidence suggests that even small dosages of phytocannabinoids can increase the number of endocannabinoids and their receptor sites, improving the effectiveness of the system as a whole. \*



# Endocannabinoid Deficiency

In human studies, ECS deficiencies have been implicated in:

- Schizophrenia
- Migraine
- Multiple sclerosis
- Huntington's
- Parkinson's
- Irritable bowel syndrome
- Anorexia
- Chronic motion sickness
- Fibromyalgia (Dunnett, 2007)
- Menstrual symptoms (Dunnett, 2007)

(reviewed in McPartland, 2014 and Russo, 2004)



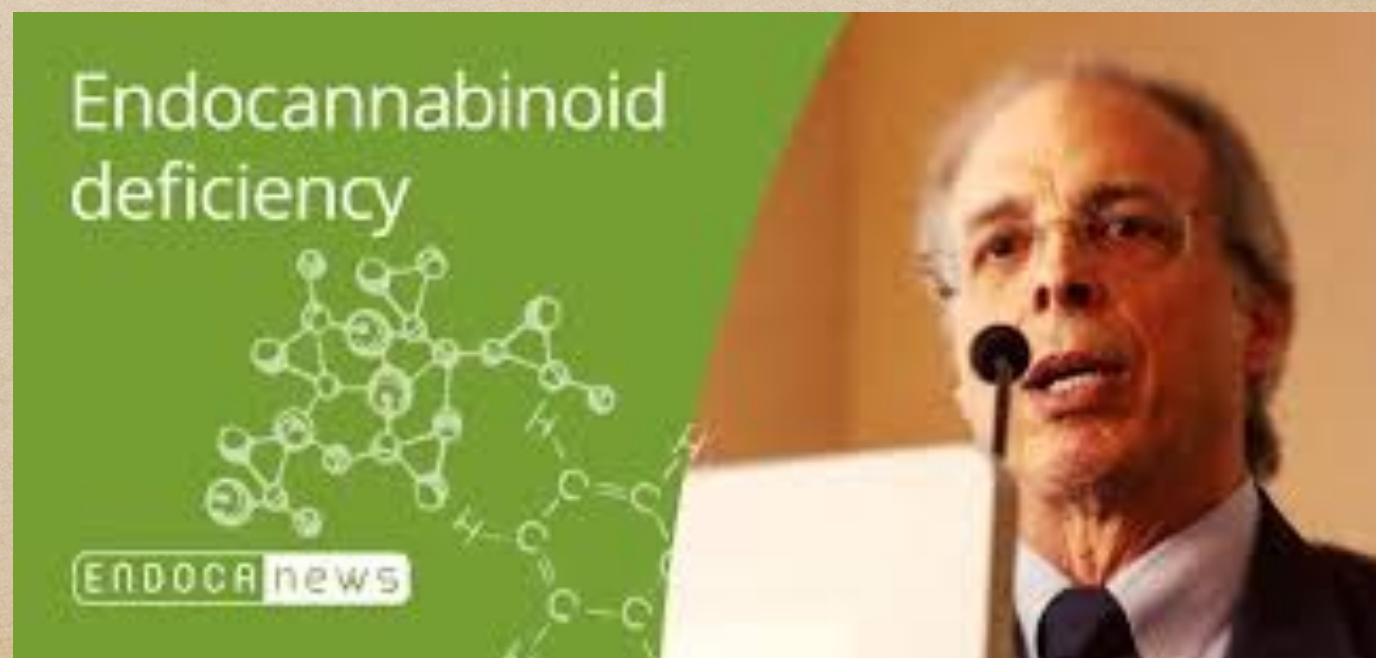
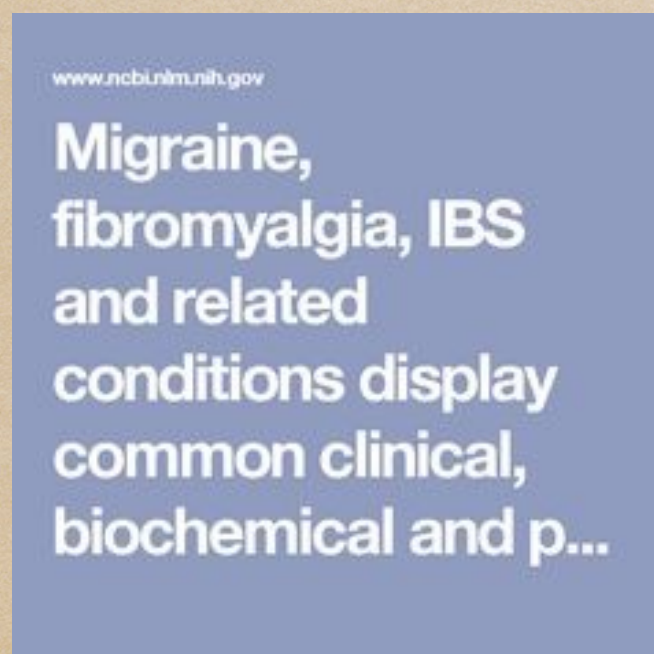
# Endocannabinoid Tone

Anandamide and 2-AG increased in body by CBD

These 2 compounds act directly on CB1 and CB2

CBD “sets the stage” for CB agonists - is a very weak agonist for CB2, but modifies receptors so other cannabinoids target CB2 more (why it counteracts high of THC)

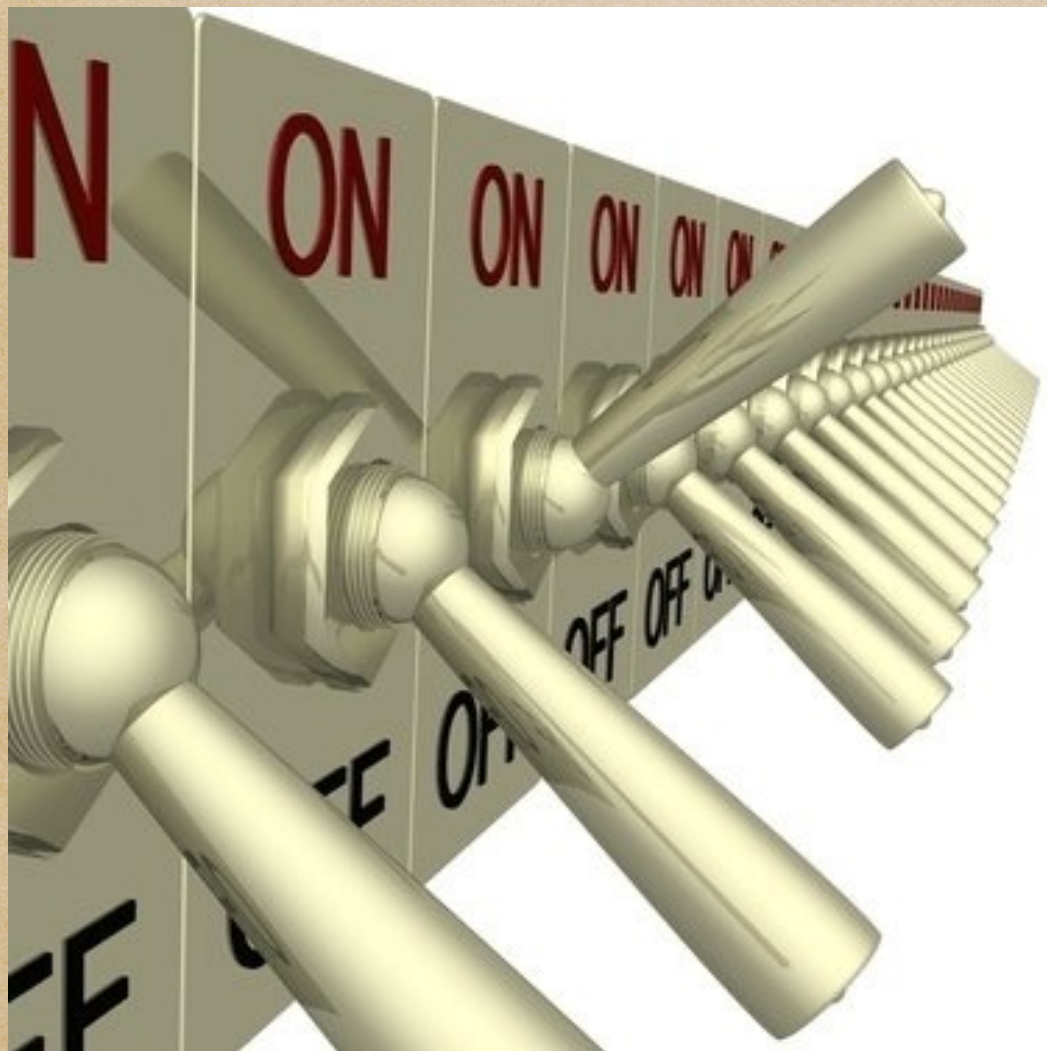
Clinical Endocannabinoid Deficiency - coined by Dr. Ethan Russo





# Gene Transcription Modulation

**Research Paper:** Differential Transcription profiles mediated by exposure to the Cannabinoids, Cannabidiols, D9 THCol in BV2 microglial cells (British Journal of Pharmacology)



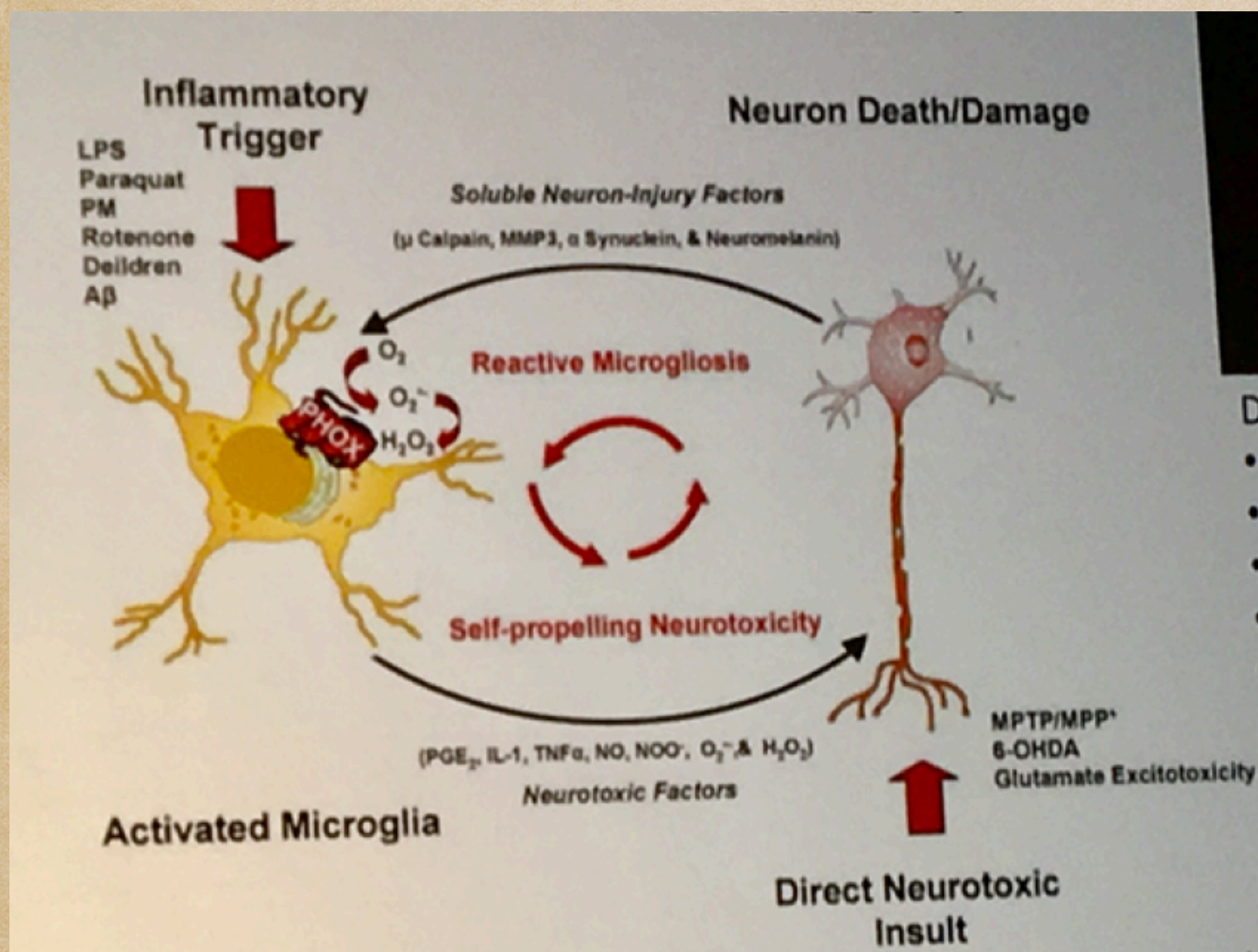
## Major Effects on Ox Stress, Inflammation, and Immunity Genes

- CBD much broader effect than THC on a transcription level
- Glutathione system strongly unregulated
- Nrf2-ARE/EhRE a BIG target
- Downregulates inflammatory cytokines
- Increased tolerance to LPS injury



# NeuroInflammation

Direct Neurotoxins  
(Glutamate Excitotoxins)



- Mercury
- Glyphosate
- Mold Toxins
- Lyme Toxins
- EMF Stress
- Dysbiotic Toxins



# Cannabinoids Modulate Neural Plasticity

## **Mechanisms by which Cannabinoids modulate Neural Plasticity**

- Depolarization-induced suppression of excitation (DSE)
- Depolarization-induced suppression of inhibition (DSI)
- Long-term potentiation (LTP)
- Long-term depression (LTD)
- Neurogenesis
  - pCREB: phosphorylated cAMP response element-binding protein
  - BDNF: brain-derived neurotrophic factor

(Fishbein, 2012)

(Lovinger, 2008)



# Federal Patent



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

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241, abstract No. 1723.\*

Mechoulam et al., "A Total Synthesis of d1- $\Delta^1$ -Tetra-  
hydrocannabinol, the Active Constituent of Hashish<sup>1</sup>," *Jour-  
nal of the American Chemical Society*, 87:14:3273-3275  
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Mechoulam et al., "Chemical Basis of Hashish Activity,"  
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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 Patients<sup>1</sup>," *Pharmacology*,  
21:175-185 (1980).

Consroe et al., "Acute and Chronic Antiepileptic Drug  
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mental Neurology*, Academic Press Inc., 70:626-637 (1980).

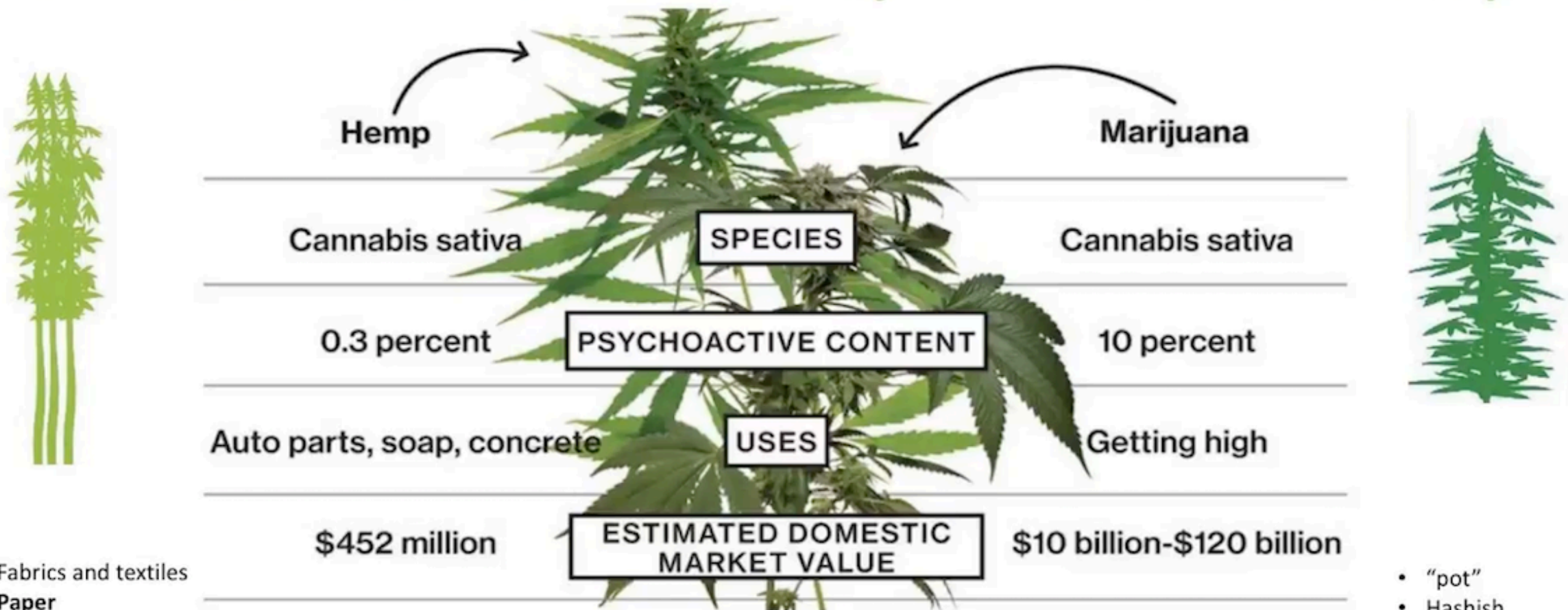
Turkanis et al., "Electrophysiologic Properties of the Can-  
nabinoids," *J. Clin. Pharmacol.*, 21:449S-463S (1981).

Carlini et al., "Hypnotic and Anti-epileptic Effects of Can-



# Cannabis and Industrial Hemp

## Difference between medicinal marijuana and Industrial Hemp



- Fabrics and textiles
- **Paper**
- Carpeting
- Home furnishings
- Construction and insulation materials
- Auto parts
- Composites
- Animal bedding
- Industrial oils

- "pot"
- Hashish
- Cannabis Oil

### PAPER INDUSTRY



Source: Pictured Modified from Herb.co





# Content Matters

- Organic
- Grown in the Earth, Under the Sun
- Non-GMO
- Whole plant
- Cannabinoids, Flavonoids, Terpenes and all the constituents
- Important that it is cultivated and prepared properly to ensure bioavailability



# Whole Plant

## **CBD Works Best Combined With Other Cannabinoids**

- Embracing the full-spectrum of cannabis' naturally occurring phytonutrients is part of a process called whole plant medicine.
- According to Franjo Grotenhermen, former Chairman of the International Association For Cannabinoid Medicines (2000-2003), "CBD is CBD." He goes on to say, "the human body does not care where the molecule comes from."
- The founders of the THC molecule, Raphael Mechoulam, discovered an interesting phenomenon called the entourage effect that explains why single CBD molecules are bad. Very briefly, the entourage effect says that ALL the cannabinoid molecules need each other to work properly, as nature designed/evolved to be.

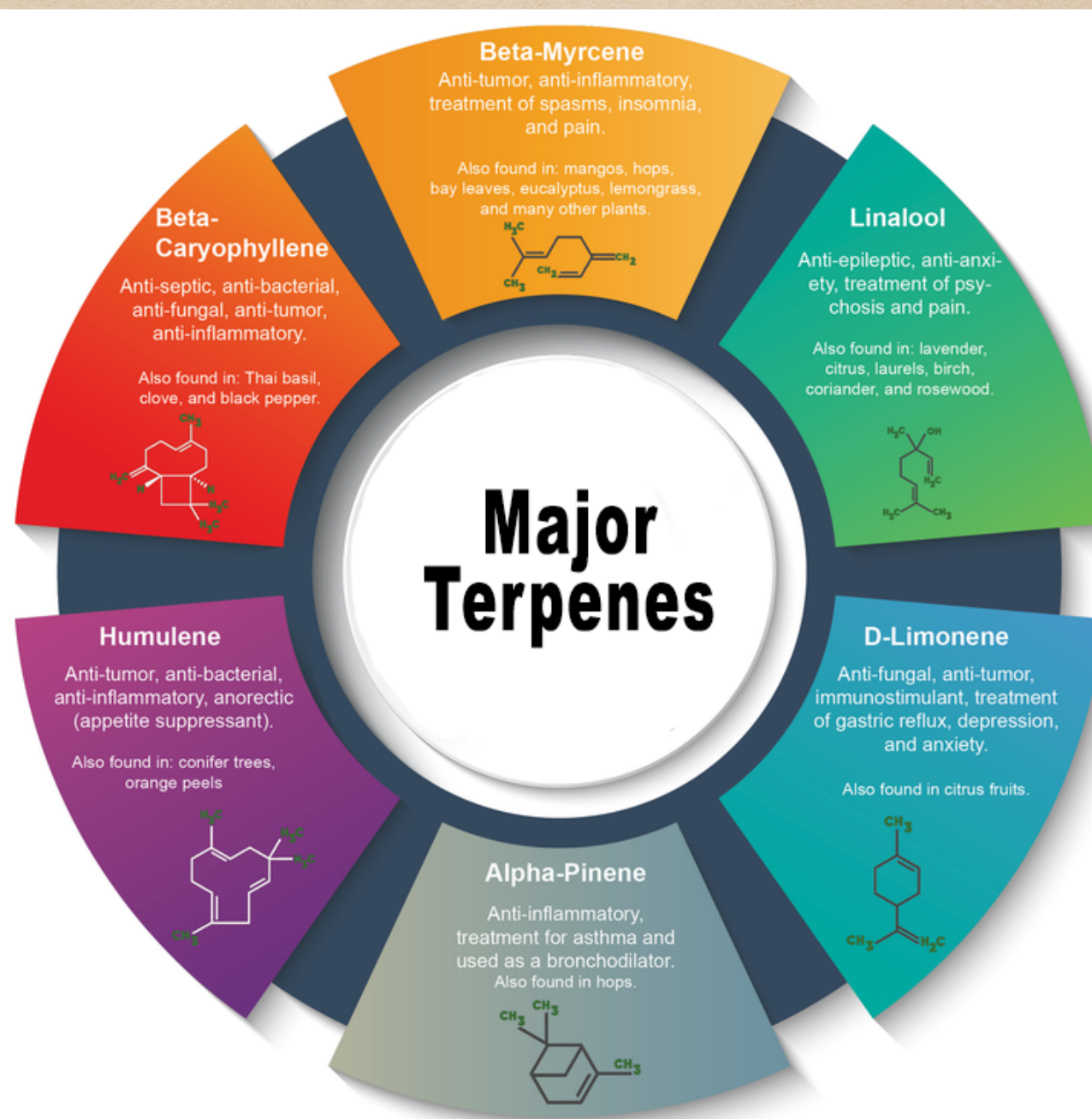


# Cannabis vs. Hemp CBD

- CBD is found in both the “drug” producing Cannabis Indica and hemp producing Cannabis Sativa.
- Hemp CBD oil is derived from industrial hemp, the C. Sativa species of cannabis, which produces nearly no amount of the cannabinoid Delta-9-tetrahydrocannabinol (THC), but does produce some amount of the cannabinoid Cannabidiol (CBD).
- Not all Hemp CBD Oil is equal
- Hemp-derived CBD *can* lack critical medicinal terpenes and secondary cannabinoids found in cannabis oil unless added in.
- Industrial hemp typically contains less cannabidiol than cannabis strains so a larger amount of hemp is required to extract a small amount of CBD, unless you are looking at delivery system where there is more absorption into the human body.



# Terpenes & Flavonoids



Terpenes are naturally occurring molecules that exist in many plants including citrus fruit rinds, many herbs, hops, and pine needles. Hemp and/or cannabis plants also have terpenes that are a naturally occurring component of the plant. There are over 100 known terpenes that can be found in the cannabis plant, and each of these can contribute to the smell, taste, and effect that the plant has on the human body.



# Terpenes

Terpenes are fragrant oils that give cannabis its aromatic diversity. They're what gives the aromatic smell.



# Flavonoids

Flavonoids are a group of phytonutrients most remarkably known for providing vivid non-green color pigments to the plant kingdom—think blue in blueberries, red in roses, etc.



# Delivery Methods

- Inhalation: Vaporizing, smoking
- NanoEnhanced Liposomal (sublingual)
- Oromucosal (tincture, oil)
- Enteral (capsules, edible, tincture if swallowed)
- Topical (salves, liniments)
- Transdermal (patch)
- Rectal



# Testing

- Potency, spectrum of Cannabinoids
- Terpene Profiling
- Flavonoid Profiling
- Pesticide Screening
- Residual Solvents
- Heavy Metal Testing
- Mycotoxins Analysis



# Final Thoughts

- More patients are looking into Cannabis for health benefits
- TCM acknowledges that all substances contain jing-qi-shen and therefore cannabinoids can be viewed as material representations of these energies.
- Biomedicine focusing on pharmaceuticals and synthetic cannabis and MD's are not herbalists
- Cannabis has been used since the beginning of time for many uses. With the discovery of the ECS, Chinese medical practitioners are positioned to benefit the ECS not only with Cannabis, but all branches of CM.



Thank You!

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