Health and Human Services Interim Committee

Utah Legislature

The Endocannabinoid System and Quality Control of Cannabis Medicines

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ASA

Key Concepts

- Cannabinoids mimic the effects of the ECS stimulation
- Mutations of the ECS may underlie certain diseases
- In basic research models: inhibition of tumor growth via specific cell-signaling pathways that regulate growth, apoptosis, angiogenesis, and metastasis
- Gold standard clinical research shows that Cannabis (marijuana) is not linked to long-term cognitive deficits or negative health effects, regardless of the amount of use.
- AHP Monograph—Standards exist that qualify it as a botanical medicine

Outline

- Research Studies
- ECS Basics
- Basic Research
- CB1 Receptor Structure
- Cannabis compounds
- Basic Product Safety for Botanicals/Herbals
- Auditing Medical Cannabis Operations

Year, Number of Studies on Cannabis and Cannabinoids

2014,2331	1997,352	1980,198	1963,10	1946,14
2013,1748	1996,273	1979,191	1962,7	1945,8
2012,1755	1995,264	1978,248	1961,8	1940,1
2011,1589	1994,186	1977,247	1960,6	1939,1
2010,1553	1993,175	1976,362	1959,5	1909,1
2009,1379	1992,143	1975,351	1958,4	1893,1
2008,1516	1991,187	1974,440	1957,1	1883,2
2007,1241	1990,157	1973,478	1956,1	1847,1
2006,1153	1989,131	1972,414	1955,2	1845,1
2005,1103	1988,119	1971,343	1954,7	1843,1
2004,885	1987,162	1970,234	1953,10	
2003,746	1986,162	1969,161	1952,3	
2002,690	1985,155	1968,111	1951,9	
2001,608	1984,160	1967,58	1950,4	
2000,501	1983,143	1966,12	1949,2	
1999,430	1982,136	1965,17	1948,4	
1998,445	1981,184	1964,17	1947,5	

More than 1,500 studies published in 2015

The Endocannabinoid System (ECS)

- Discovered with the help of phytocannabinoids *(Cannabis Sativa, Voacanga Africana, Rhodenderon Anthpogonoides, Radula Marginata,* and *Helichrysum Umbraculigerum)*
- Consists of endocannabinoids (anandamide,2-AG), cannabinoid receptors (GPCRs), and enzymes for synthesis and catabolism
- *"Eat, sleep, relax, forget, and protect"*
- Clinical Endocannabinoid Deficiency (CECD; Russo 2004)

Helichrysum Umbraculigerum

Rhodenderon Anthpogonoides

Cannabis Sativa

Radula Marginata

Voacanga Africana

Cannabinoid Receptor Genetics

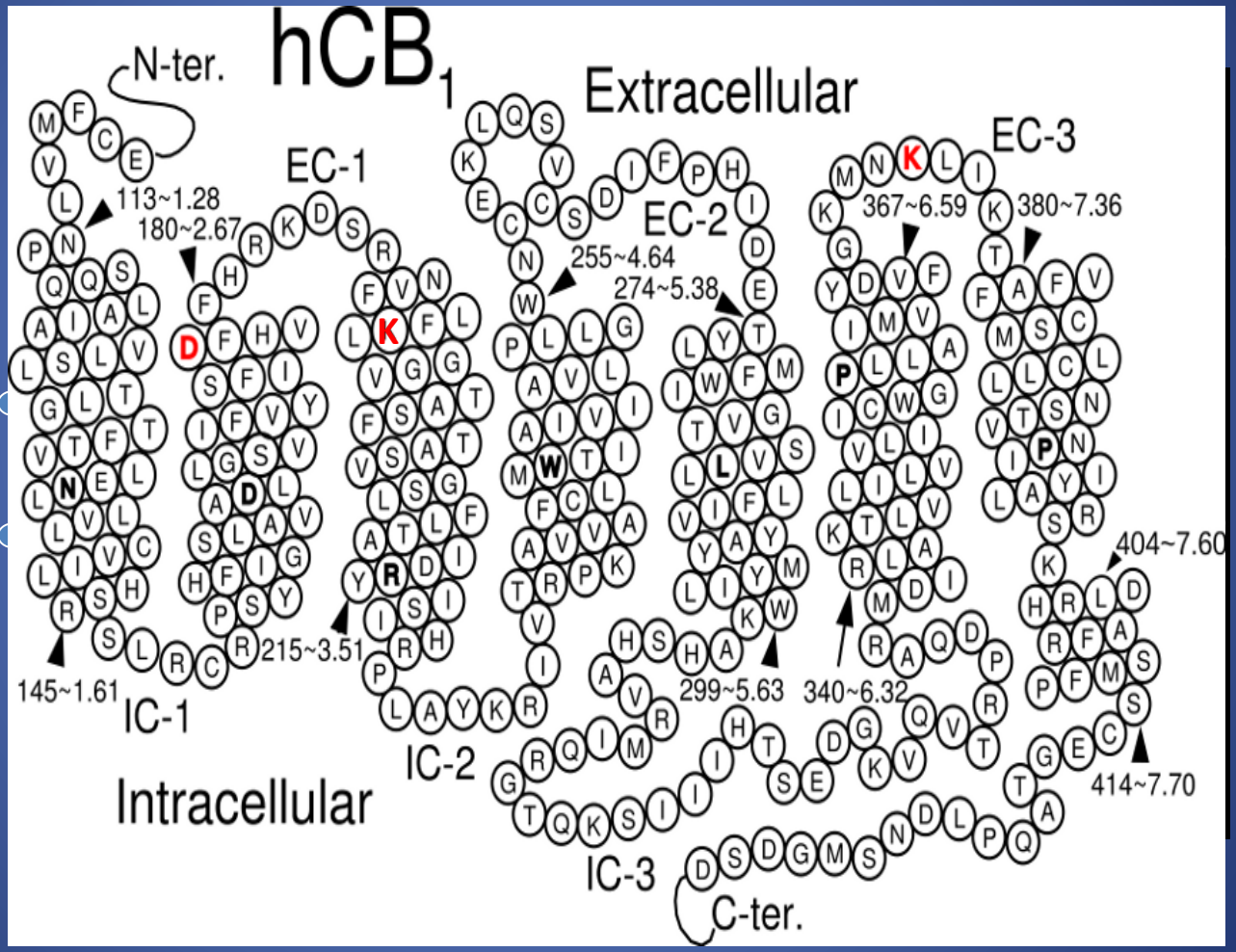
- CNR1 encodes CB1 localized on 6q14-q15 (Hoehe et al. 1991)
- CNR2 encodes CB2 localized on 1p36.1 (Valk et al. 1997)

Mutation	Description	Disease Associations	References
CNR1 Trinucleotide repeat in 3' UTR	AAT repeat	Schizophrenia, substance abuse disorders, Parkinson's disease, inverse relation between number of repeats and working memory performance	Zhang et al., 2004; Comings et al., 1997; Ujike et al., 2002; Barrero et al., 2005, Ruiz-Contreras et al., 2013
CNR1 SNPs or Haplotypes	rs6454674; rs806380; rs806377; rs1049353; rs806379; rs1535255; rs2023239;rs806368; rs806369; rs1049353; rs4707436; rs12720071; rs3505747	Substance abuse disorders, depression, anxiety and eating disorders, obesity, schizophrenia, attention deficit disorder	Hopfer et al., 2006; Zuo et al., 2009; Zhang et al., 2004; Juhasz et al., 2009; Lazary et al., 2009; Ho et al., 2011, Okahisha et al., 2011, Mutombo et al., 2012, Marcos et al., 2012
CB2 SNPs	rs2502992, rs2501432	Low bone mineral density or osteoporosis associated in at least 3 distinct human populations	Huang et al., 2009; Karsak et al., 2005; Karsak et al., 2009; Yamada et al., 2007

Cannabinoid Receptor Structure

Extracellular

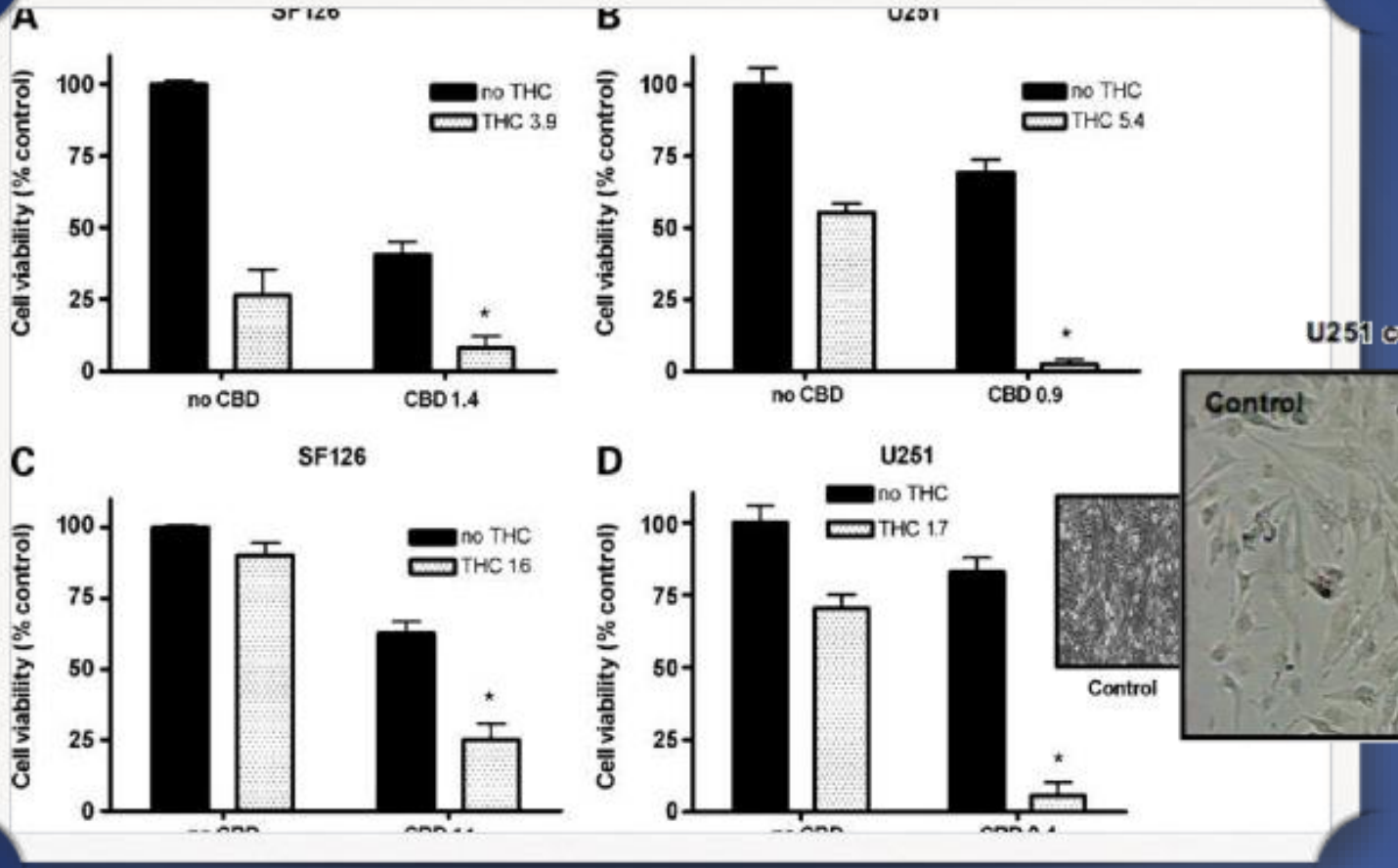
Intracellular



3-Dimensional Figure from *Trends Endocrin Metabol 2003,14:431*

20 HOUR TIMELAPSE VIDEO (23 SECONDS)

THC Selectively Kills Cancer Cells



Cell Culture Experiments

HUMAN BRAIN CANCER CELL LINES

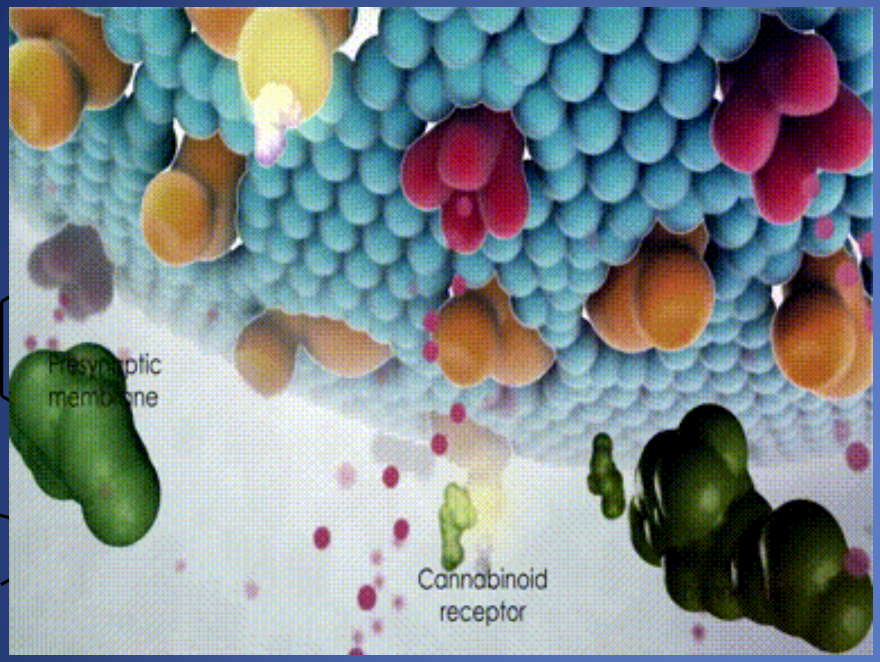
Long Term Use and Side Effects

Pope, H. G., Gruber, A. J., Hudson, J. I., Huestis, M. A., & Yurgelun-Todd, D. (2001). Neuropsychological performance in long-term cannabis users.

NEW ZEALAND Study :No dose dependency, did not control not binge drinking. They took into account schizophrenia but not any other mental illness and any traumatic injuries (i.e., Concussions, stroke). All their effects are explained are explained with socio-economic factors. No neuroimaging, neurochemical, or anatomical correlates presented.

Chronic cannabis use by adolescent boys does not appear to be linked to later physical or mental health outcomes that were measured regardless of the amount of use during adolescents (**Bechtold J, et al.. Chronic Adolescent Marijuana Use as a Risk Factor for Physical and Mental Health Problems in Young Adult Men. Psychol Addict Behav. 2015)**

Δ^9-tetrahydrocannabinol (THC)

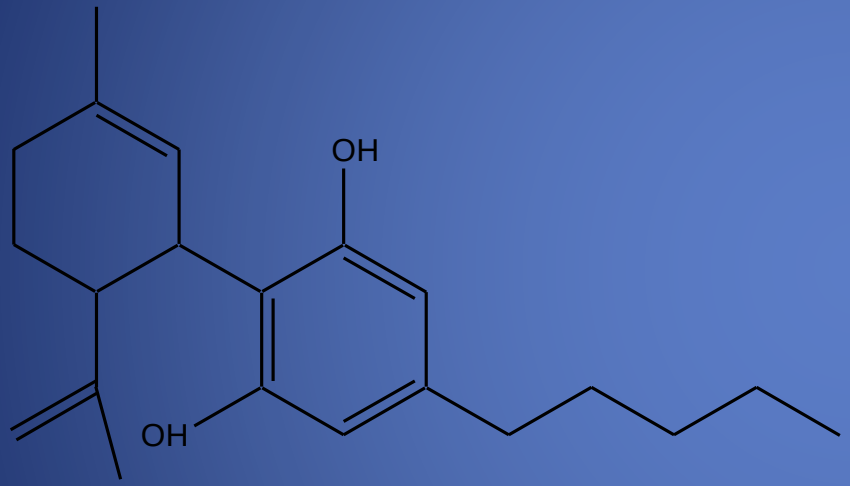


delta-9-tetrahydrocannabinol (THC)

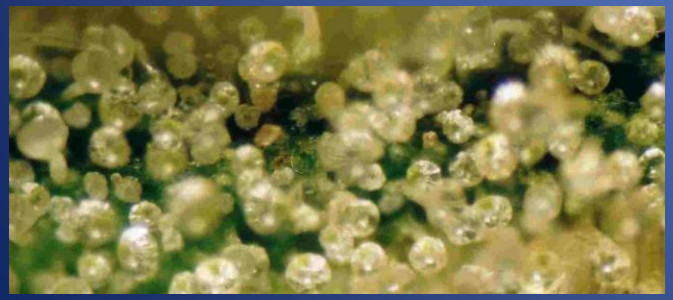
- **Isolated and identified (Gaoni & Mechoulam 1964)**
- **Analgesic via CB_1, CB_2 , etc.**
- Anti-emetic
- Bronchodilatory (Williams 1976)
- Antispasmodic
- **Neuroprotective antioxidant (Hampson 1998)**
- THC inhibits PGE-2 synthesis (Burstein1973)
- **THC has 20X power of hydrocortisone (Evans 1991)**
- THC stimulates LO (Fimiani 1999)
- THC not a COX-1 or COX-2 inhibitor (Stott 2005)
- Synthetic form approved by FDA as Marinol® in 1985

Photo EBR, courtesy of Bedrocan

Cannabidiol (CBD) I



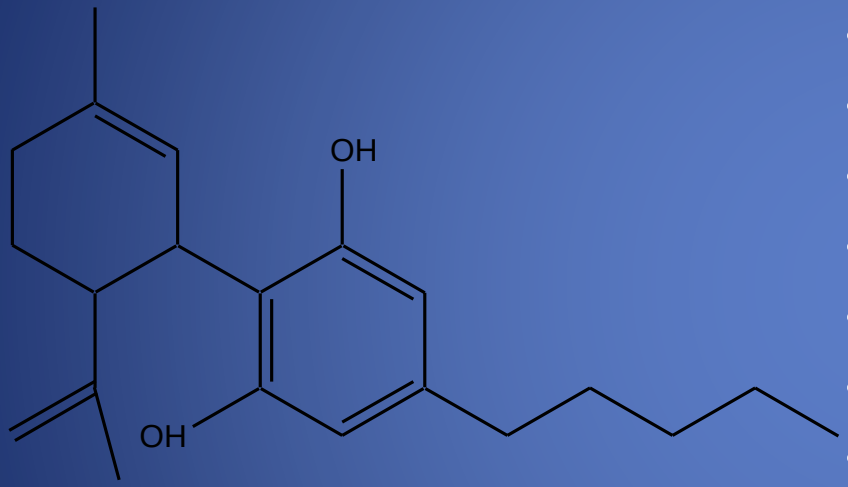
cannabidiol



G5 CBD trichomes Photo DJP. Slide courtesy of EBR

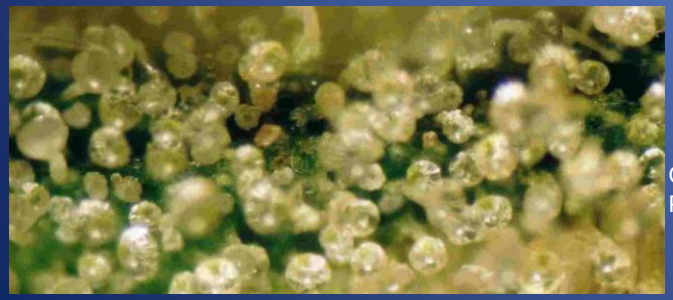
- **Isolated 1940 (Adams), but identified positively in 1963 (Mechoulam & Shvo)**
- Binds CB_1 with Ki 4900 nM and CB_2 4200 nM, but shows unique ability to antagonize these receptors with K_B in low nM range (Thomas 2007)
- **Neuroprotective AO, strongly inhibits glutamate excitotoxicity, also anti-oxidant > Vitamins C and E (Hampson et al. 1998)**
- **Now known to be a VR_1 agonist with EC_{50} 3.2-3.5 µM (Bisogno et al. 2001)**
- Inhibits uptake of the AEA, and weakly inhibits its hydrolysis (Bisogno et al. 2001)
- "In a manner of interpretation, CBD may be considered the first clinical agent that **modulates endocannabinoid** function." (Russo 2003)
- **Alerting vs. THC in clinic (Nicholson 2004), and experimentally in rat hypothalamus and dorsal raphe nucleus (Murillo-Rodriguez et al. 2006)**
- CBD may have its own endogenous receptor. It is an antagonist at GPR55 and GPR18 (McHugh et al. 2010)

Cannabidiol (CBD) II



cannabidiol

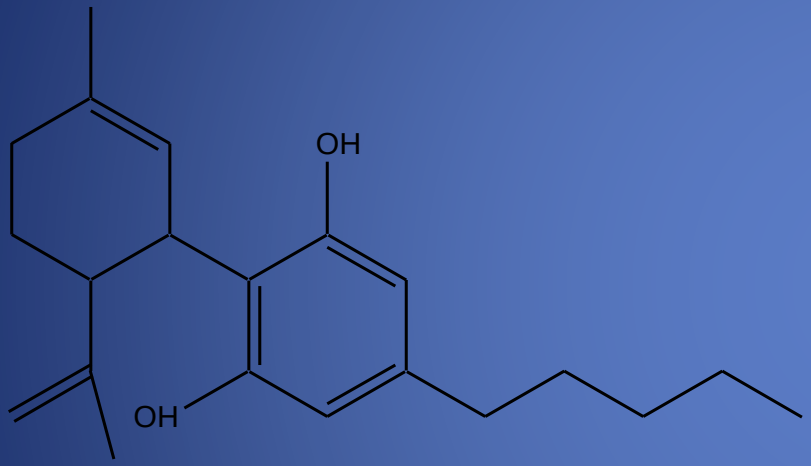
- **Anticonvulsant**
- **Anti-anxiety**
- Anti-nausea
- Lowers intraocular pressure
- Anti-dystonic
- Antipsychotic
- Mood regulator
- Appetite suppressant
- Blocks 11-hydroxylation of THC
- **Cytotoxic in breast cancer (IC_{50} 6-10.6 µM) and many other cancer cell lines via increased apoptosis mediated via CB_2 activiation $TRPV_1$-induced increase in Ca^{++} (Ligresti 2006)**



G5 CBD trichomes
Photo DJP. Slide courtesy of EB

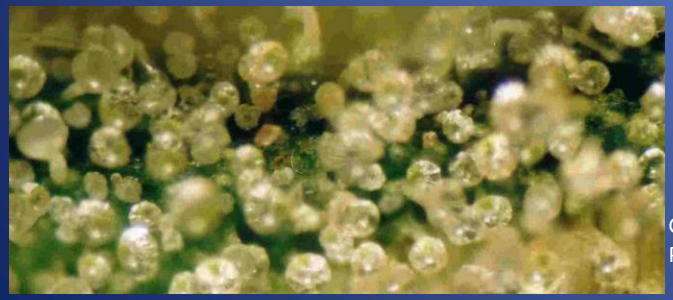
µ

Cannabidiol (CBD) III



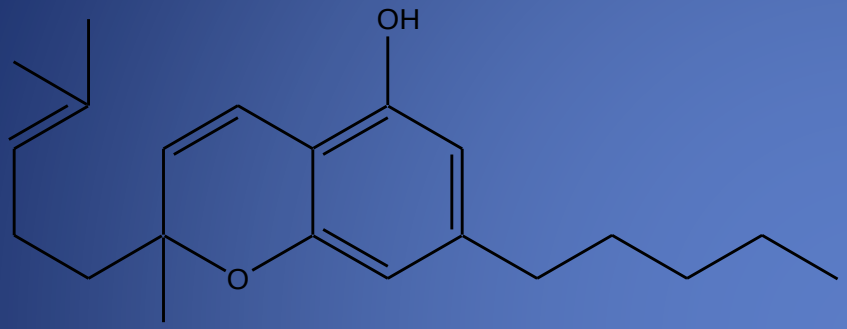
cannabidiol

- Antagonizes tumor necrosis factor alpha (TNF-α) in rodent rheumatoid arthritis (Malfait 2000)
- Not COX-1 or COX-2 inhibitor (Stott 2005)
- **Modulates side effects of THC (Russo-Guy 2006)**
- **Displays agonistic activity at 5-HT1A receptor (Russo-Parker 2005), possible basis for observed anxiolysis (Resstel 2009), CVA reduction (Mishima 2005) & improvement of cognition in hepatic encephalopathy (Magen 2009).**
- **Enhances adenosine receptor A2A signaling via inhibition of an adenosine transporter (Carrier 2006), suggesting an important therapeutic role in various inflammatory and chronic pain states**
- Prevents prion accumulation and neuronal toxicity (Dirikoc 2007)
- **CBD extract showed greater antihyperalgesia in rat model over pure CBD (Comelli 2008), decreased allodynia, improved thermal perception & NGF levels, decreased oxidative damage (Comelli 2009)**
- **Powerful activity against MRSA (MIC 0.5-2 µg/ml) (Appendino 2008)**



G5 CBD trichomes
Photo DJP. . Slide courtesy of EB

Cannabichromene (CBC)



cannabichromene

Photo EBR, courtesy of GWP

- Identified (Gaoni & Mechoulam 1966)
- "Inactive" on adenylate cyclase inhibition (Howlett 1987)
- **Anti-inflammatory (Wirth et al. 1980)**
- **Analgesic, though less potent than THC (Davis & Hatoum 1983)**
- Reduced THC toxicity in mice (Hatoum et al. 1981)
- **Antibiotic/antifungal (ElSohly 1982; McPartland & Russo 2001)**
- **Cancer cytotoxic agent (Ligresti et al. 2006)**
- Comparable to mustard oil in stimulating TRP_{A1}-mediated Ca^{++} in HEK 293 cells (50-6- nM) (De Petrocellis 2008)
- **GWP CBC extract demonstrated pronounced antidepressant effect in rodents (Deyo & Musty, 2003)**
- Forms a fraction of 6% of minor cannabinoids in Sativex BDS
- CBC-rich cultivar available

THC and CBD Part 1

- *CBD decreased anxiety caused by THC (Karniol et al., 1974)*
- *CBD slightly increased time to onset, intensity, and duration of THC intoxication (Hollister and Gillespie, 1975)*
- *CBD attenuated THC euphoria (Dalton et al., 1976)*
- *CBD reduced anxiety provoked by THC (Zuardi et al., 1982)*
- *CBD improved sleep and decreased epilepsy (Cunha et al., 1980; Carlini and Cunha, 1981)*
- *CBD decreased cortisol secretion and had sedative effects (Zuardi et al., 1993)*

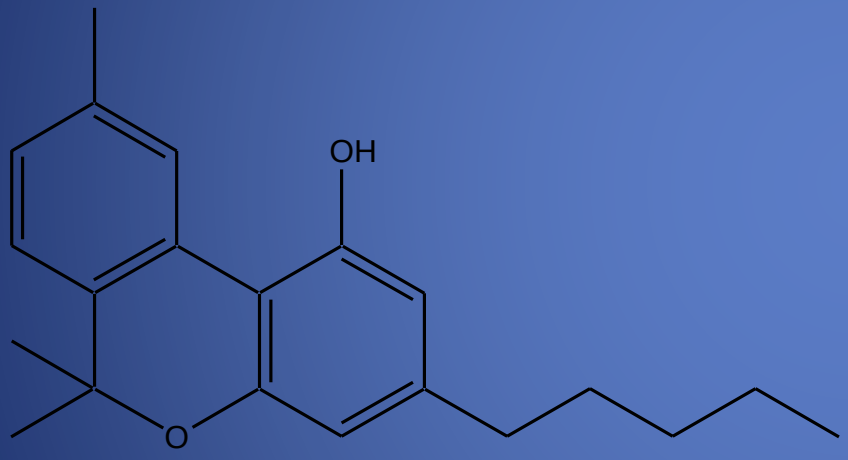
THC and CBD part 2

- *CBD provided antipsychotic benefits (Zuardi et al., 1995)*
- *CBD reduces the appetitive effects of THC (Morgan et al., 2010)*
- *CBD plus THC imparted synergistic inhibition of human glioblastoma cancer cell growth and apoptosis (Marcu et al., 2010)*
- *Sativex compared to THC greater pain relief and improvement in sleep (Notcutt et al., 2004)*
- *Sativex compared to THC extract reduced cancer-related pain (Johnson et al., 2010)*
- *Sativex compared to THC reduced abnormalities in psychomotor performance associated with schizophrenia (Roser et al., 2009)*

Cannabigerol (CBG)

Photo EBR, courtesy of GWP

- **Identified/synthesised (Gaoni-Mechoulam 1964)**
- K_i 440 nM at CB_1 and 337 nM at CB_2 (Gauson/Pertwee 2007)
- **GABA uptake inhibitor > THC or CBD (Banerjee et al. 1975)**
- **Analgesic activity > THC, anti-erythemic >>THC, blocks LO > THC (Evans 1991)**
- **Modest antifungal activity (ElSohly 1982)**
- Effective against human oral epithelioid carcinoma in high dosage (Baek et al. 1998)
- **Antidepressant in tail suspension model (Musty-Deyo 2006)**
- Anti-hypertensive (Maor 2006)
- Next most effective phytocannabinoid vs. breast cancer after CBD (Ligresti 2006)
- Inhibits keratinocyte proliferation in psoriasis (Wilkinson-Williamson 2007)
- **Powerful activity against MRSA (MIC 0.5-2 µg/ml) (Appendino 2008)**
- **Potent α-2 adrenoreceptor agonist (for pain, ?↓reuptake) and less potent 5-HT_{1A} antagonist (antidepressant?) (Cascio 2010)**
- TRPM8 antagonist (De Petrocellis 2010) for application in prostate cancer
- Forms a fraction of 6% of minor cannabinoids in Sativex BDS
- CBG-only cultivar available



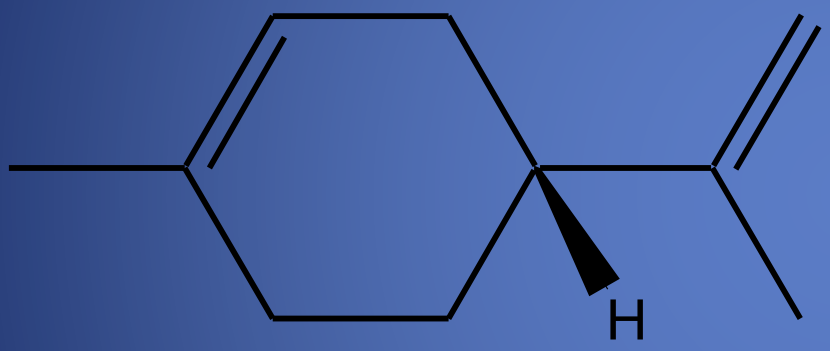
cannabinol (CBN)

Cannabinol (CBN)

- K_i at CB_1 211.2 nM, at CB_2 126.4 nM (Rhee 1997)
- Non-enzymatic THC oxidation product
- **Sedative (Musty 1976)**
- **Anticonvulsant (Turner 1980)**
- **Anti-inflammatory (Evans 1991)**
- **Antibiotic (McPartland-Russo 2001), potent against MRSA (MIC 1µg/ml)(Appendino 2008)**
- TRPV2 (hi-threshold thermosensor) agonist (EC 77.7 µM)(Qin 2008)
- Inhibits keratinocyte proliferation (low micromolar) via CBR-independent mechanism, suggesting utility in psoriasis (Wilkinson 2007)
- Stimulates recruitment of quiescent mesenchymal stem cells in marrow (10 µM) promoting bone formation (Scutt 2007)
- **Inhibited breast cancer resistance protein (IC 145 µM)(Holland 2008)**

Photo EBR, courtesy of GWP

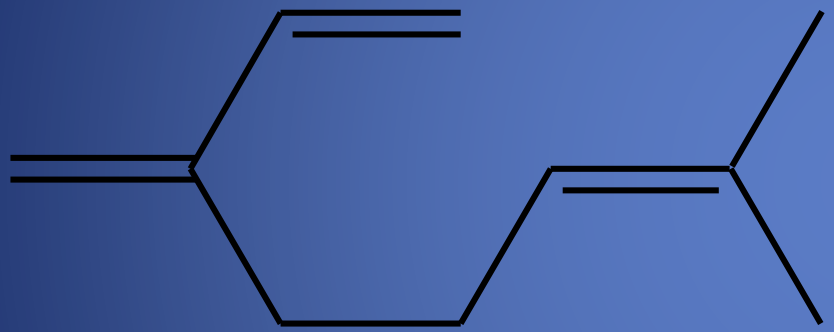
d-limonene



Limonene

EBR, courtesy of GWP

- Monoterpene, precursor to other terpenoids via species-specific synthetic schemes
- Markedly anxiolytic (as orange EO) in rodent models (Carvalho-Freitas 2002; Pultrini 2006)
- **Potent antidepressant and immune stimulator in humans via ambient inhalation (Komori et al. 1995)**
- **Lemon EO vapour anxiolytic, AD in mice, with ↑5-HT in PFC, DA in HC, mediated via 5-HT$_{1A}$ (Komiya 1999)**
- **Produced apoptosis of breast cancer cells in Phase II trials (Vigushin et al. 1998)**
- **Citrus EO effective against dermatophytes (Ramadan 1996; Sanguinetti 2007; Singh 2010)**
- GRAS FEMA 1965; FDA



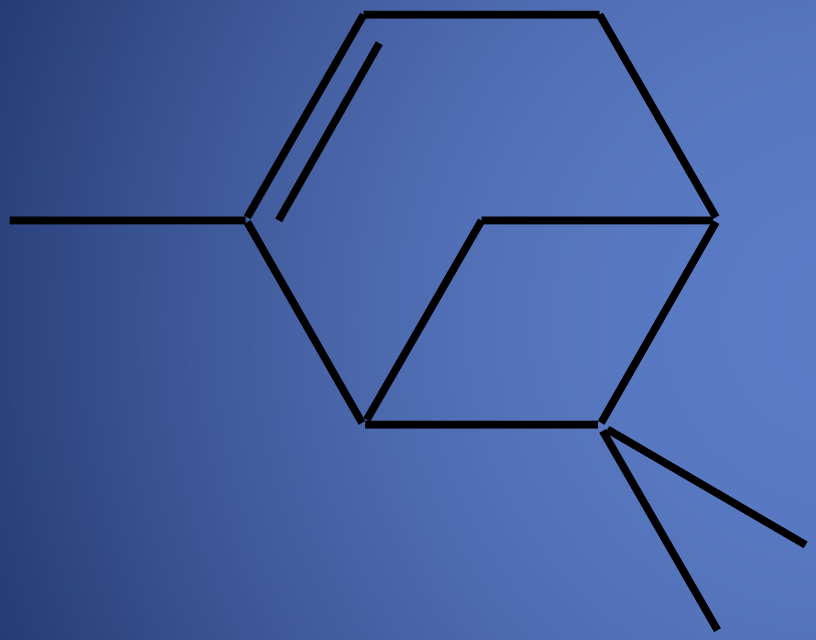
Myrcene

ρ-myrcene

- **Blocks inflammation via PGE-2 (Lorenzetti et al. 1991)**
- **Analgesic, antagonized by naloxone (Rao et al. 1990)**
- **Sedating (Wichtl 2004), muscle relaxant and potentiated barbiturate sleep time in mice (do Vale et al. 2002)**
- **Blocks hepatic carcinogenesis by aflatoxin (de Oliveira et al. 1997)**
- GRAS FEMA 1965, FDA

EBR, courtesy of GWP

α-pinene

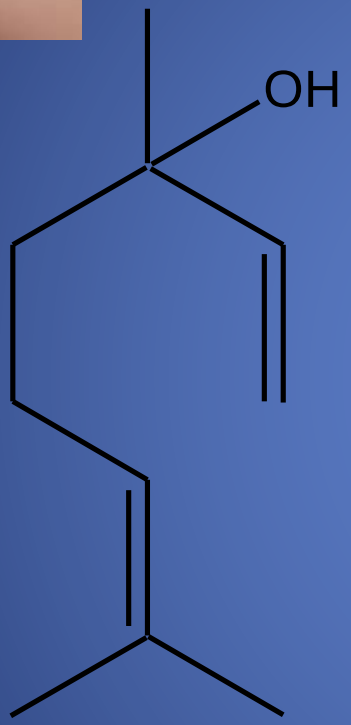


alpha-pinene

- **Anti-inflammatory via PGE-1 mechanism (Gil et al. 1989)**
- **Bronchodilatory in humans (Falk et al. 1990)**
- **Acetylcholinesterase inhibitor, aiding memory (Perry et al. 2000), IC_{50} 0.44 mM (Miyazawa 2005)**
- **Major component of *Sideritis* EO against MRSA et al. (Kose 2010); *Salvia* EO component (Ozek 2010)**
- GRAS FEMA 1965; FDA

EBR, courtesy of GWP

D-linalool

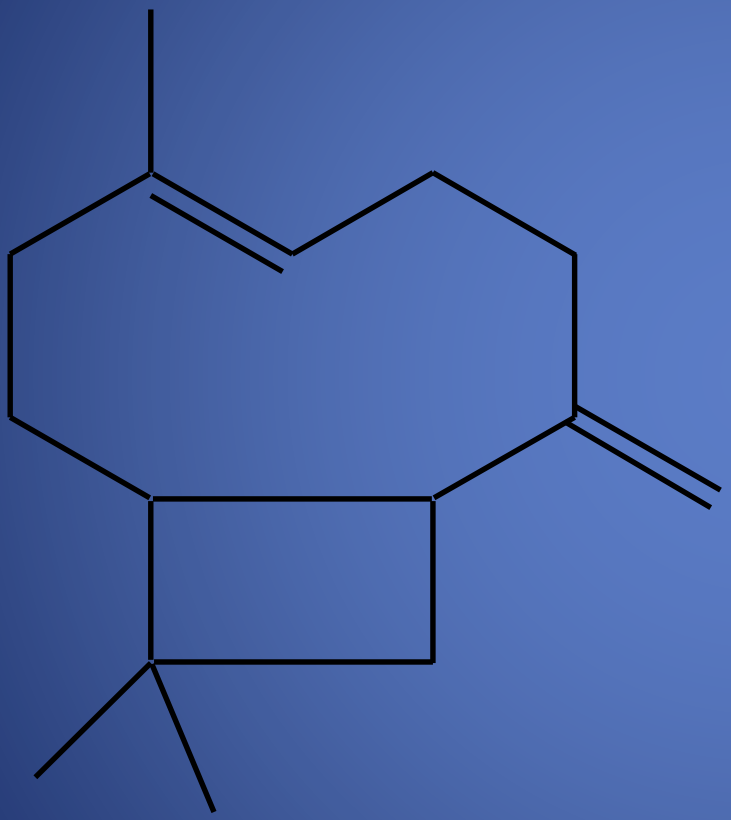


d-linalool

- **Anti-anxiety (Russo 2001)**
- **Sedative on inhalation in mice (Buchbauer et al. 1993)**
- **Local anesthetic (Re et al 2000), equal to procaine, menthol (Ghelardin 1999)**
- ↓ K+-stimulated Glu release and uptake in mouse synaptosomes (Brum (2001)
- **Agonist at TRPM8, but at mM concentrations (Beherndt 2004)**
- **Anticonvulsant/anti-glutamatergic (Elisabetsky et al. 1995); AC in *Ocimum* EO against pentylenetetrazole, picrotoxin & strychnine (Ismail 2006)**
- Potent anti-leishmanial (do Socorro 2003)
- **Produced hot-plate analgesia in mice ($p<0.001$), reduced by adenosine A2A antagonist (Peana 2006)**
- **Moderately ↓ proliferation of human breast adenoca., but reversed doxorubicin resistance (Ravizza 2008).**
- Antinociceptive at high doses in mice via ionotropic glutamate receptors (Batista 2008)
- "Overall, it seems reasonable to argue that the modulation of glutamate and GABA neurotransmitter systems are likely to be the critical mechanisms responsible for the sedative, anxiolytic and anticonvulsant properties of linalool and E0s containing linalool in significant proportions." (Nunes 2010, p. 303).
- As lavender EO, decreased opioid usage in gastric banding surgical patients (Kim 2007)
- GRAS FEMA 1965, FDA

EBR, courtesy of GWP

β-caryophyllene



beta-caryophyllene

EBR, courtesy of GWP

- **Anti-inflammatory via PGE-1 comparable potency to phenylbutazone (Basile et al. 1988); EO with BC content = etodolac and indomethacin (Ozturk 2005)**
- **Gastric cytoprotective (Tambe et al. 1996)**
- Attracts predatory green lacewings, but inhibits insect herbivory (Langenheim 1994)
- Anti-malarial (Campbell 1997)
- **Selective CB_2 full agonist (100 nM)(Gertsch 2008)**
- **<5 mg/kg po produced AI/analgesic effects in wild-type, but not CB_2 knockout mice (Zimmer 2009)**
- GRAS FEMA 1965; FDA

Cannabis and Opiates

The ECS is proposed to interact through:

- The release of opioid peptides by CBs and the release of eCBs by opioids (Russo 2008, Abrams 2011).
- Existence of a direct receptor-receptor interaction and cellular pathways – allosteric modification of heterodimers.
- Clinically, THC may enhance the pain relieving effects of opiates, lowering the amount of an opiate necessary for relief (Abrams 2011).
- Lower opiate OD statistics in Colorado.
- Surveys suggest Cannabis used to decrease abuse of other drugs (alcohol, nicotine, and opiates).
- Adolescent Exposure to Chronic THC Blocks Opiate Dependence in Maternally Deprived Rats.

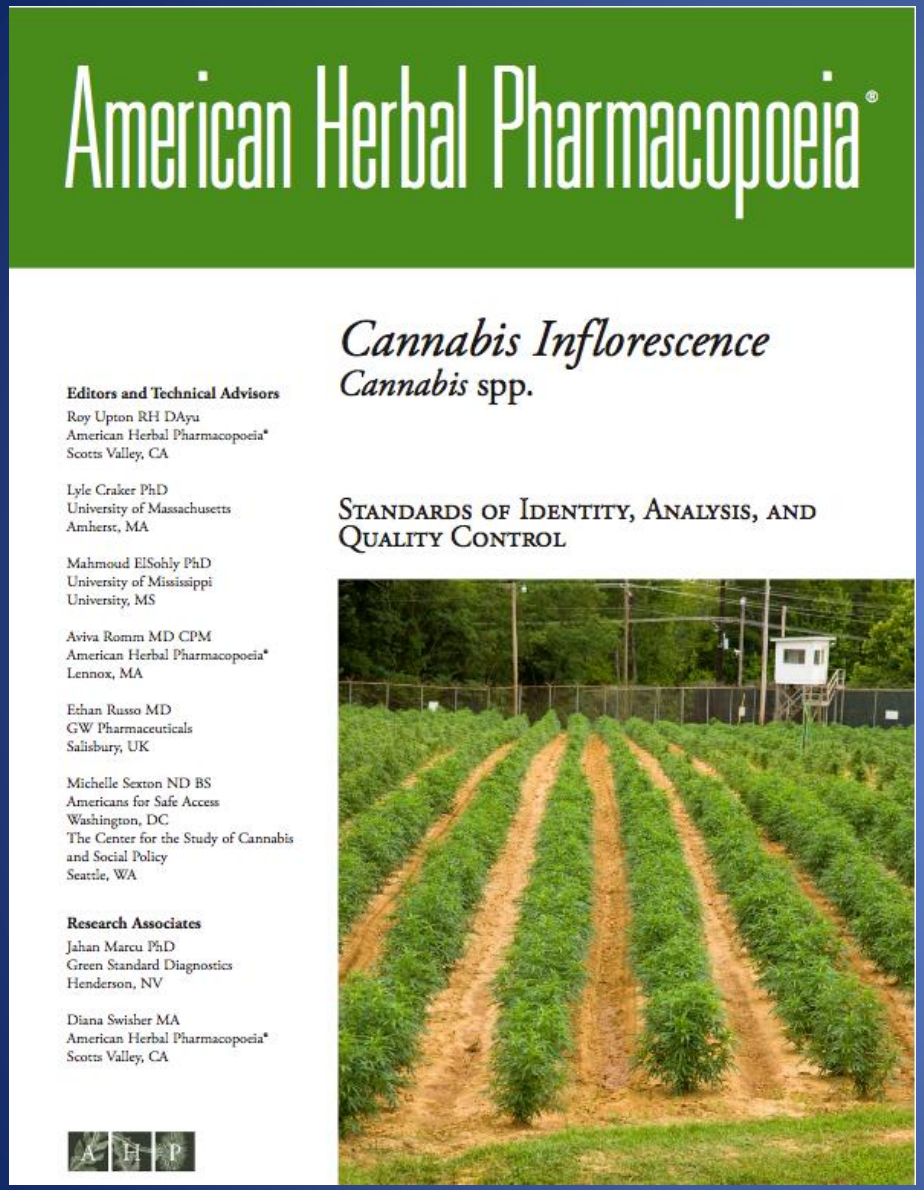
Brief History of Medical Cannabis in the United States

1996 – First Laws – criminal exemptions

2002-2004 – ASA & patients pass distribution laws in the Bay Area

2010 – Colorado commercial distribution

A need for product safety because…



PATIENTS, PROVIDERS, AND REGULATORS BENEFIT

Standards for identifying the quality, purity and potency of the plant that would qualify it as a botanical medicine.

And it's becoming mandatory!

American Herbal Pharmacopeia (AHP)

Established regulatory guidelines for:

- Purity
- Identification of products being sold
- Proper packaging and storage protocols

Herbal-AHP.net

American Herbal Products Association (AHPA) Recommendations to Regulators

- Cultivation and processing
- Manufacturing, packaging & labeling
- Dispensing (distribution) operations
- Laboratory practices

AHPA

AMERICAN HERBAL PRODUCTS ASSOCIATION

AHPA.org

Patient Focused Certification (PFC)

- Ensures compliance, involves a physical audit, annual surprise audit

•Recall strategy, adverse event reporting, proper labeling, batch/lot tracking, mandatory product safety testing

- Documentation and staff training

- Patientfocusedcertification.org

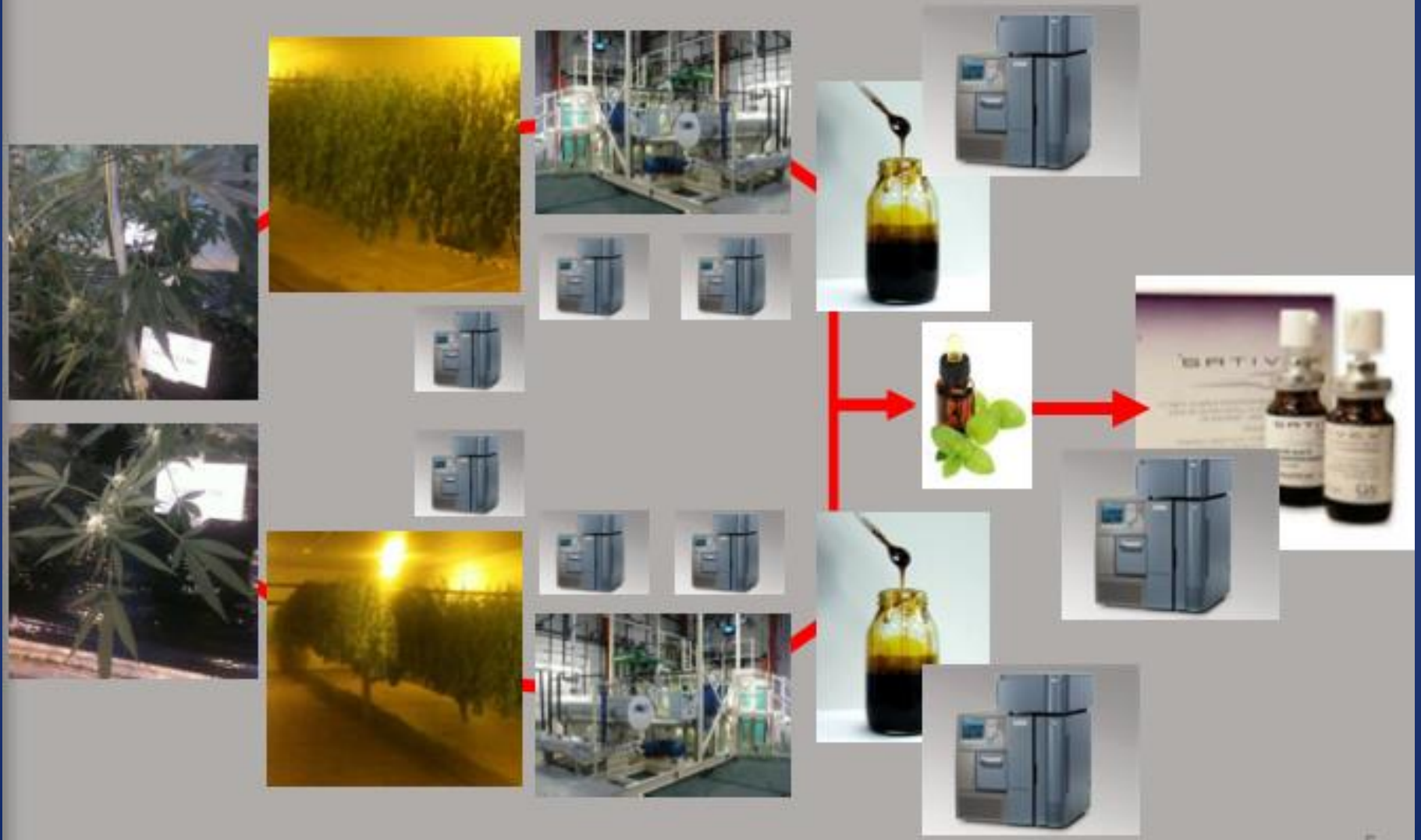
Patient Focused Certification (PFC)

- Non-profit, third party certification for the medical cannabis industry
- Americans for Safe Access Foundation (ASAF)
- Certification based on quality standards for medical cannabis products and businesses issued by the American Herbal Products Association (AHPA) and the American Herbal Pharmacopeia (AHP) Cannabis monograph.
- Online PFC courses-CTI

State Laws can Interfere with Product Safety

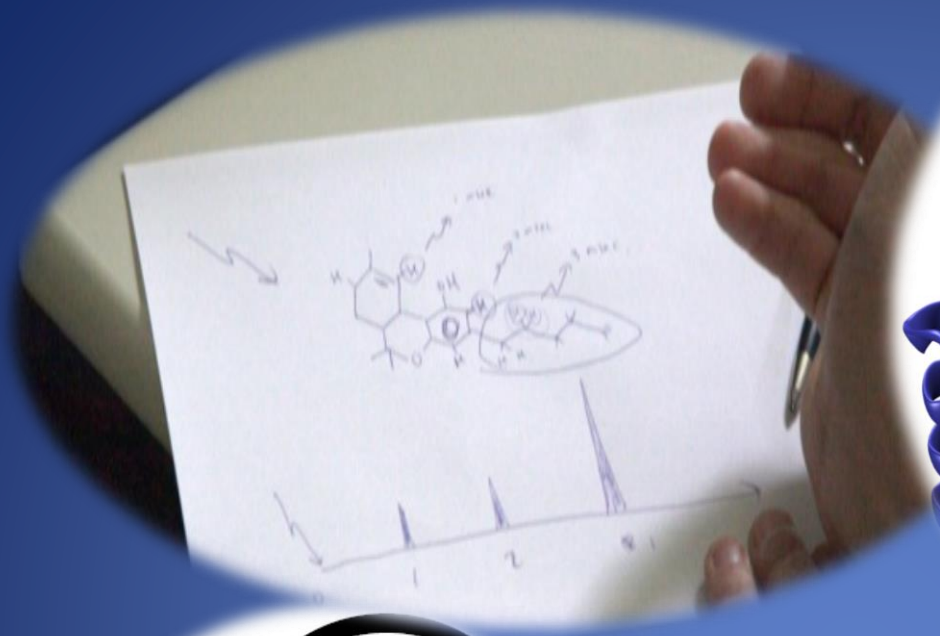
- Adverse event recording and reporting
- Recall plan
- Security
- Waste Disposal
- The rules and requirements also differ from state to state

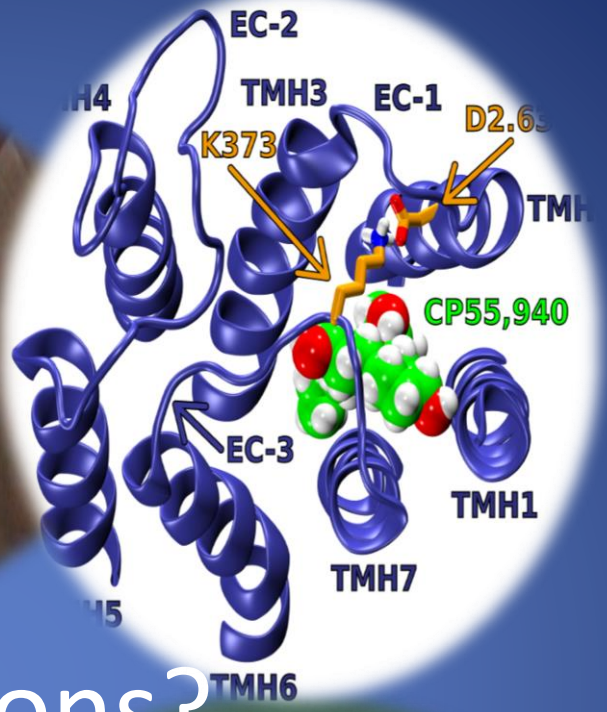
The process and QC is a little more complex



Summary

- The ECS: Eat, Sleep, Relax, Forget, and Protect
- Cannabinoids are prescribed to treat neurodegenerative disorders, not cause them
- Cannabis is inherently safe; commercialization is complicated
- 3rd Party Certification ensures basic product safety





Questions?

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