Indication-Specific Cannabis Chemovarieties

delta-9-tetrahydrocannabinol (THC)

Ethan Russo, MD
Medical Director

Limonene

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Δ⁹-tetrahydrocannabinol (THC)

- Isolated and identified 1964 (Gaoni & Mechoulam)
- $K_i = 53.3$ at CB₁, 75.3 at CB₂ (Felder 1995)
- Analgesic & antipruritic (Neff 2002)
- Bronchodilatory (Williams 1976)
- Neuroprotective antioxidant (Hampson 1998)
- THC has 20X A-I power of ASA, 2X A-I power of hydrocortisone (Evans 1991)
- Muscle relaxant
- Antiemetic
- Primary psychoactive component
- THC not a COX-1 or COX-2 inhibitor (Stott 2005)
- ↓ β-amyloid (Eubanks 2006)
Cannabidiol (CBD) I

- Isolated 1940 (Adams), but identified positively in 1963 (Mechoulam & Shvo)
- Hardly binds $\text{CB}_1$, but shows unique ability to antagonize the receptor in low nM range (Thomas 2007)
- Works as a negative allosteric modulator on $\text{CB}_1$ (Laprairie 2015)
- Neuroprotective AO, strongly inhibits glutamate excitotoxicity, also anti-oxidant > Vitamins C and E (Hampson et al. 1998)
- Now known to be a TRPV1 agonist (like AEA) with $\text{EC}_{50}$ 3.2-3.5 $\mu$M (Bisogno et al. 2001)
- Inhibits uptake of the AEA, and weakly inhibits its hydrolysis (Bisogno et al. 2001)
- Alerting vs. THC in clinic (Nicholson 2004)
Cannabidiol (CBD) II

- Anticonvulsant (Cunha; Jones 2010)
- Anti-anxiety (Crippa 2010)
- Cytotoxic in breast cancer ($IC_{50}$ 6-10.6 μM) and many other cancer cell lines while being cytopreservative for normal cells (Ligresti 2006)
- Antagonist at GPR55 and GPR18 (McHugh et al. 2010)
Cannabidiol (CBD) III

• Antagonizes tumor necrosis factor alpha (TNF-α) in rodent rheumatoid arthritis (Malfait 2000)
• Not COX-1 or COX-2 inhibitor (Stott 2005)
• Displays agonistic activity at 5-HT$_{1A}$ receptor (Russo-Parker 2005), possible basis for observed anxiolysis (Resstel 2009; Soares 2010), CVA reduction (Mishima 2005), nausea (Limebeer 2009), & 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 stimulates bone fracture healing (Kogan 2015)
Odds ratios* in red are statistically significant. 

*p-value relates to comparison of proportion of patients Sativex v Placebo.


Presence of CBD in nabiximols produced clinical improvement over high-THC extract and placebo.


Results imply a markedly better therapeutic index and safety margin for nabiximols/Sativex over pure THC.
Tetrahydrocannabivarin (THCV)

- Identified (Gill/Paton/Pertwee 1970)
- CB₁ antagonist at low doses (Thomas et al. 2005), but CB₁ agonist at higher doses (Pertwee 2007)
- Produces weight loss, decreased body fat and serum leptin concentrations with increased energy expenditure in obese mice (Cawthorne 2007; Riedel 2009)
- Displays prominent anticonvulsant properties (Hill 2010)
- Decreased edema & hyperalgesia (Bolognini 2010)
- THCV-predominant cultivar available (de Meijer)
Tetrahydrocannabinolic Acid (THCA)

- THC form in fresh, unheated cannabis flowers
- Insecticidal (Sirikantaramas 2005)
- Anti-inflammatory/anti-TNF-alpha (Verhoeckx 2006)
- Anticonvulsant in mice only at 200 mg/kg (Karler 1978)
- However, certain clinicians note benefit in epilepsy at low doses of THCA even in total absence of THC or CBD
Cannabidiolic Acid (CBDA)

- Predominant phytocannabinoid in fresh hemp
- Natural herbicide (Shoyama 2008), as long known in retting pond usage
- Powerful anti-emetic via 5-HT\textsubscript{1A} stimulation (Bolognini 2013)
- Anticonvulsant for seizures of partial onset, in Phase II clinical trials
- Promising for treating tumors

\[\text{cannabidiolic acid}\]
Certain cannabis terpenoids are analgesic and/or anti-inflammatory, mood enhancing, and modulate THC effects producing synergy with phytocannabinoids.
D-Limonene

- Potent antidepressant and immune stimulator in humans via ambient inhalation (Komori et al. 1995), lowering HADS and allowing d/c of AD Rx.
- Lemon EO vapor 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)
- Human pulmonary uptake 70% (Falk 1990)
- GRAS FEMA 1965; FDA
Myrcene

- Blocks inflammation via PGE-2 (Lorenzetti et al. 1991)
- Analgesic in mice, antagonized by naloxone (Rao et al. 1990)
- Sedating (Wichtl 2004), muscle relaxant and potentiated barbiturate sleep time in mice at high dose (De Vale et al. 2002): The “Couch-lock Factor”
- Blocks hepatic carcinogenesis by aflatoxin (de Oliveira et al. 1997)
- GRAS FEMA 1965, FDA
α-Pinene

- Anti-inflammatory via PGE-1 mechanism (Gil et al. 1989)
- Bronchodilatory in humans, with 60% uptake, with rapid distribution and metabolism (Falk et al. 1990)
- Acetylcholinesterase inhibitor, aiding memory (Perry et al. 2000)
- Wide spectrum antibiotic (Nissen 2010)
- GRAS FEMA 1965; FDA

~45%
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 (Ghelardini 1999)
- Anticonvulsant/anti-glutamatergic (Elisabethsky et al. 1995)
  - Produced hot-plate analgesia in mice (p<0.001)
  - GRAS FEMA 1965, FDA
**β-Caryophyllene**

- 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)
- Selective CB$_2$ full agonist (100 nM) (Gertsch 2008a), suggesting dietary use at 5 mg/kg AI (Gertsch 2008b)
- <5 mg/kg po produced AI/analgesic effects in wild-type, but not CB$_2$ knockout mice (Zimmer 2009)
- ? Utility in contact dermatitis (Karsak 2007)
- GRAS FEMA 1965; FDA
Outline of an Ideal Cannabis Classification Scheme

• Combines shape, content and purpose
• Basic class based on primary cannabinoid (e.g. Type I for THC)
• Plant morphology (e.g., broad-leaf compact vs. tall, spindly)
• Specific cannabinoid content
• Specific terpenoid content
• Scent
• Taste (when vaporized)
• Uses/Effects (patient-oriented)

Photos: EBR
Pinetrak
Type I
(THC-predominant)
High in everything
Classic OG X Haze
Type I
Terpenoid-rich, balanced
Type I
“Pinene”: clarity
Type II: (THC = CBD)

Fruity Pop

Rich in multiple components
Type II: Sweet Surrender
general purpose, low sedation
Creamsicle Skunk
Type II
“Inspirational”
Type II Blue Dream balanced, clear, good for work or study
Type II Legend
burns, epilepsy
Type III (CBD-predominant)
Legend
pain, inflammation
addiction
Type III
Lemon CBD
Depression, anxiety
Type III: High CBDV, High Limonene, High Caryophyllene, High Linalool

Applications:
Wide Spectrum
Anticonvulsant
Type I High THCV, High Limonene, High Caryophyllene

Applications:

- Neuropathic pain
- Hepatic fibrosis