Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads

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Cannabis sativa and the Endocannabinoid System

- It began with a plant called cannabis----
- Cannabis makes glandular trichomes, that in turn produce THC

- THC binds to a receptor, CB₁ that also binds endogenous cannabinoids, the “endocannabinoids,” anandamide and 2-arachidonylglycerol.
Cannabis sativa L.

- Food (seed)
- Fuel (seed oil)
- Fiber (stalks)
- Farmacy (unfertilized female flowering tops)

Photo EBR, with permission, Hash, Marijuana and Hemp Museum, Amsterdam, June 2001
Cannabis Trichomes on Flowers and Leaf

Sessile trichome on leaf surface
Scale bar = 20 µm

These trichomes are quantitatively and qualitatively different!

Sphere V = \( \frac{4}{3} \pi r^3 \)
Trichome volume in mm\(^3\):

5.4 \times 10^{-4} \quad \text{vs.} \quad 4.19 \times 10^{-6}
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)
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Cannabis plant

Fan leaves:
- Cannabinoids (CB): 0.05%
- Sesquiterpenoids >> Monoterp.
- Flavonoids
- Canniprene (up to 0.2%)

Stem:
- CB: 0.02%
- Cellulose

Roots:
- CB: 0%
- Triterpenoids
- Alkaloids

Unfertilized Flower:
- CB: up to 30%
- Monoterp >> Sesquiterp.: up to 4% total

Fertilized Flower:
- CB: up to 13%

Capitate glandular trichomes:
- CB: up to 60%
- Monoterp >> Sesquiterp.: up to 8% total

Seeds:
- CB: 0%
- Terpenoids: 0%
- Edestin protein: 35%
- Essential fatty Acids: 35%
- Cannabisin B
- Caffeoyltyramine

Seed Sprouts:
- as above + cannflavin A

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Phytocannabinoids

delta-9-tetrahydrocannabinol
cannabinol
cannabidiol
cannabichromene
cannabigerol
tetrahydrocannabinol
cannabinol
cannabidiol
cannabinol
cannabigerol monomethyl ether

delta-9-tetrahydrocannabinolic acid
cannabidiolic acid

cannabidiolic acid

cannabidiolic acid

cannabidiolic acid

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Pentyl Cannabinoid Synthesis

Propyl Cannabinoid Synthesis

The same enzymes process propyl substrates:
An example of “Nature’s Law of Stinginess” (Mechoulam)
or
“Enzymatic substrate promiscuity” (ESP)
(© 2010 EBR)

Δ⁹-tetrahydrocannabinol (THC)

- Isolated and identified 1964 (Gaoni & Mechoulam)
- $K_i=53.3$ at $\text{CB}_1$, 75.3 at $\text{CB}_2$ (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)
- ↓ $\beta$-amyloid (Eubanks 2006)
Cannabidiol (CBD) I

- Isolated 1940 (Adams), but identified positively in 1963 (Mechoulam & Shvo)
- Hardly binds CB₁, but shows unique ability to antagonize the receptor in low nM range (Thomas 2007)
- Works as a negative allosteric modulator on CB₁ (Laprairie 2015)
- Neuroprotective AO, strongly inhibits glutamate excitotoxicity, also antioxidant > Vitamins C and E (Hampson et al. 1998)
- Now known to be a TRPV1 agonist (like AEA) with EC₅₀ 3.2-3.5 µM (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-HT₁A 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)
Misconceptions about Cannabidiol (CBD)

- A tiny amount is enough (actually more is better)
- It is not psychoactive.
- It is a sedative (Alerting vs. THC in clinic (Nicholson 2004), and sedation may be operative with high doses, drug-drug interactions or terpenoid effects, i.e., myrcene)
- It is “legal in all 50 states”
- It turns into THC in the body (Merrick 2016) (Russo 2017) (actually upregulates anandamide/ECS)
CBD
Natural History


Figure 1. Cannabidiol (CBD) Production, Biosynthesis, and Metabolism. CBD is biosynthesized in hemp or drug chemovars of Cannabis sativa, and is produced in greatest concentration in capitate glandular trichomes in the unfertilized female flowering tops of the plant. Its main precursor is olibolic acid and oliboly pyrophosphate, which produce cannabigerolic acid and then cannabidiolic acid (CBD) via catalysis by CBDA synthase, an enzyme co-dominant with Δ^2^-tetrahydrocannabinolic acid synthase (THCA). Subsequently, decarboxylation via light exposure, heating, or aging results in CBD. In vivo, first-pass hepatic metabolism produces 7-hydroxy-cannabidiol, whose specific pharmacology has yet to be ascertained. While exposure to strong acids can produce an isomerization of CBD to tetrahydrocannabinol (THC), this reaction does not occur in vivo in humans (all images by E.B.R.).
Cannabigerol (CBG)

- GABA uptake inhibitor > THC or CBD (Banerjee et al. 1975)
- Antidepressant in tail suspension model (Musty-Deyo 2006)
- Lowers BP and IOP
- Decreases keratinocytes in psoriasis (Wilkinson 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)
- Stimulates several TRP channels (de Petrocellis 2010, 2011)
Cannabichromene (CBC)

- Produced by a recessive gene
- Anti-inflammatory (Wirth et al. 1980)
- Analgesic, though less potent than THC (Davis & Hatoum 1983)
- Antibiotic/antifungal (ElSohly 1982; McPartland & Russo 2001)
- Cancer cytotoxic agent (Ligresti et al. 2006)
- GWP CBC extract demonstrated pronounced antidepressant effect in rodents (Deyo & Musty, 2003)
- Active on various TRP channels (de Petrocellis 2010, 2011)
- Demonstrates FAAH-inhibition, boosting AEA levels (Bisogno 2001)
Tetrahydrocannabivarin (THCV)

- Identified (Gill/Paton/Pertwee 1970)
- CB$_1$ antagonist at low doses (Thomas et al. 2005), but CB$_1$ 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)
- Lacks AE liabilities of inverse agonists (McPartland 2015)
- THCV-predominant cultivar available (de Meijer)
Cannabidivarin (CBDV)

- Inhibits DAGL (De Petrocellis 2010), biosynthetic enzyme of 2-AG
- Anticonvulsant in hippocampal slices, comparable to phenobarbitol and felbamate (Hill 2010)
- In Phase II clinical trials for seizures of partial onset

Photo EBR, courtesy of GWP
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), but clinical reports in epilepsy (Sulak/Goldstein) indicate efficacy at much lower dosages (Russo 2016)
- Has high affinity for CB₁ (Rock 2013), but is unable to cross the BBB (Moreno-Sanz 2016)
- Increased cell survival and neurite morphology in PD model (Moldzio 2012)
- Reduced N&V reactions in rodents (Rock 2013)
Cannabidiolic Acid (CBDA)

- Predominant phytocannabinoid in fresh hemp
- Natural herbicide (Shoyama 2008), as long known in retting pond usage
- Produces COX-inhibition at high doses (Takeda 2008)
- Powerful anti-emetic via 5-HT$_{1A}$ stimulation (Bolognini 2013; Rock 2013)
- Promising for treating tumors (historical data)
Cannabigerol Monomethylether (CBGM)

- Commonly encountered in cannabis
- No specific pharmacology has been tested
Cannabinol (CBN)

- Non-enzymatic THC oxidation product, stable
- Mildly sedative (Musty 1976)
- Anticonvulsant (Turner 1980)
- Anti-inflammatory (Evans 1991)
- Antibiotic (McPartland-Russo 2001), potent against MRSA (MIC 1μg/ml) (Appendino 2008)
Certain cannabis terpenoids are analgesic and/or anti-inflammatory, mood enhancing, and modulate THC effects producing synergy with phytocannabinoids.
Monoterpenoids

Myrcene

Limonene

alpha-pinene

beta-pinene

d-linalool

ocimene

terpinolene

alpha-terpineol

alpha-terpinene

gamma-terpinene

alpha-phellandrene

cymene

camphene

delta-3-carene

fenchol

1,8-cineole

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α-Pinene

- A bicyclic monoterpenic, the most widely distributed terpenoid in Nature (Noma 2010).
- Anti-inflammatory via PGE-1 (Gil et al., 1989).
- **Bioavailability via inhalation (60%)** with rapid metabolism and redistribution (Falk 1990), with bronchodilation effect in humans.

Wide spectrum antibiotic (Nissen 2010). Equally effective against MRSA and other resistant bacteria as vancomycin (Kose et al., 2010): Active versus *P. acnes* and *Staph* spp. (Raman et al., 1995), and for MRSA, *Cryptococcus neoformans* *Candida albicans* biofilms (Rivas da Silva et al., 2012).

- Dramatically lowered MIC of ciprofloxacin, erythromycin and triclosan against the gastroenteritis pathogen, *Campylobacter jejuni* (Kovac 2015).
- Beneficial against *Leishmania amazonensis* (Rodrigues 2015), and vectors of malaria, dengue and Japanese encephalitis (Govindarajan et al., 2016).

- Increased mouse motility after inhalation **13.77%** (Buchbauer 1993). At 10 µL/L concentration produced **an anxiolytic effect in the elevated plus maze**, with general brain distribution (Kasuya 2015). In chronic inhalation over 5 days, anxiolytic effects were maintained (Satou 2014).

- Most notable for **acetylcholinesterase inhibition** (Perry et al., 2000)(Miyazawa 2005), which serves to reduce or eliminate short-term memory impairment by THC.

- **Protected rat astrocytes from H2O2 damage by 69%** (Elmann 2008).

- Pinene has also been suggested as a **modulator of THC overdosage** (Russo 2011).

- Chronic exposure led to decreased melanoma growth in mice at 180 ng/L (1 ppm) in ambient air, a dose too low to directly affect tumor (Kusuhara 2012), a **health-promoting effect is known in Japan as “Shinrin-yoku” or “forest bathing.”**

A direct synergistic and isobolographic benefit was observed in combination with paclitaxel versus non-small-cell A549 lung carcinoma cells with evidence of apoptosis (Zhang 2015). α-Pinene inhibited BEL-7402 human hepatoma cell growth 79.3%, (Chen 2015) equivalent to that from 5-FU.
β-Myrcene

- Blocks inflammation via PGE-2 (Lorenzetti et al. 1991)
- Sedating (Wichtl 2004), muscle relaxant and potentiated barbiturate sleep time in mice at high dose (do Vale et al. 2002)
- Primary “couch-lock” factor in cannabis (Russo 2011)
- Blocks hepatic carcinogenesis by aflatoxin (de Oliveira et al. 1997)
- Analgesic in mice, antagonized by naloxone (Rao et al. 1990) (Paula-Freire 2013) confirmed myrcene 10 mg/kg po reduced pain behavior in both phases of the formalin test for longer that morphine (four hours) ,abrogated by naloxone administration, supporting an opioid mechanism of action.
- In human chondrocyte culture, myrcene inhibited NO production (Rufino 2015), suggesting therapeutic application in osteoarthritis.
- In rats (Bonamin 2014), oral myrcene 7.5 mg/kg benefited peptic ulcers via multiple
- In mice, 200 mg/kg ip 10 days prevented ischemic/reperfusion oxidative cerebral injury (Ciftci 2014).

Celery leaf
*Apium graveolens*: 34%

Celery leaf

myrcene
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)
- Citrus EO effective against dermatophytes (Ramadan 1996; Sanguinetti 2007; Singh 2010)
- Human pulmonary uptake 70% (Falk 1990)
- Concentrations of 400 µg/ml inhibited biofilm formation of the pathogen Streptococcus pyogenes SF370 and S. nutans, which produces dental caries, (Subramenium 2015).
- Limonene 10 mg/kg po reduced hyperalgesia in mice induced by intrathecal administration of HIV glycoprotein toxin gp120 (Piccinelli 2016).
- Produced apoptosis of breast cancer cells in Phase II trials (Vigushin et al. 1998)
- In women with pre-operative breast cancer, an oral intake of 2 g of d-limonene a day produced a breast tissue mean concentration of 41.3 µg/g of tissue (Miller 2013).
- At 100 ppm induced apoptosis in Bcl-2 human colon cancer (Chidambara Murthy 2012).
- Limonene 10 mg/kg po reduced inflammation scores, weight loss and TNF-α in ibuprofen-induced rat colitis, as well as decreasing peripheral IL-6 inflammatory marker in elderly humans receiving a daily supplement (d’Alessio 2013).
- At high concentrations, limonene prevented oxidative damage in human lens epithelial cells (Bai 2016), suggesting therapeutic use to prevent cataracts.
- Limonene is an agonist at A$_{2A}$ adenosine receptors (Park) and could synergize activity with both THC (direct activator) and CBD (uptake inhibitor via competition for the nucleotide binding site of the ENT1 transporter) (Carrier 2006)
- Limonene 50 µM increased mitochondrial biogenesis, activated the AMPK energy regulator, increased brown adipocyte markers PGC-1α UCP1, and induced “browning” of 3T3-L1 adipocytes by activating β-3-AR and ERK signaling pathway (Lone 2016), suggesting a putative role in obesity treatment.
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** (Elisabetsky et al. 1995)
- Produced hot-plate analgesia in mice (p<0.001)
- Linalool-incorporated nanoparticles are being explored as a novel anti-cancer agent (Han 2016).
Ocimene

- A common component of West Coast (Elzinga 2015) and Dutch chemovars (Fischedick 2010)
- Associated with EOs with anticonvulsant, antifungal, and anti-tumoral effects, but rarely tested on its own.
- Is a social regulation factor in honeybees (Kennell 2016)
Terpinolene

- Cyclic monoterpane, a common component of some commercial chemovars
- Demonstrated to prevent LDL oxidation (of interest in treatment of atherogenesis and CAD) (Grassman 2005)
- Concentration of 0.05% markedly reduced AKT1 expression in K562 human CML cells and significantly stimulated apoptosis (Okumura 2012)
- Sedative in mice at 0.1 mg in air, reducing motor activity to 67.8% (Ito 2013)
- Subjective reports in humans suggest more stimulation in cannabis, possibly attributable to acetylcholinesterase inhibition (Bonesi 2010)
- Also antifungal, larvicidal (Aydin 2013)
- A subactive antinociceptive/AI dose 3.125 mg/kg po in rats synergized with diclofenac, and reduced hyperalgesia, an effect blocked by ketanserin, suggesting mediation via 5-HT$_{2A}$ (Macedo 2016)
Δ³-Carene

- A bicyclic monoterpenoid alkene
- High-exposure leads to irritation of skin and lungs (Falk 1991), with rapid metabolism and high adipose tissue affinity. Exposure is common in new homes (Krol 2014).
- Carene was rapidly absorbed, distributed and metabolized in human volunteers after oral administration (Schmidt 2015).
- A low concentration (5 µM) stimulated mineralization in mouse osteoblastic cells (Jeong 2008).
- Carene demonstrated larvicidal activity against vectors of malaria, dengue, and filariasis (Govindarajan 2016).
- Carene content was judged to be a marker of “sativa” cannabis chemovars (Hazekamp 2016).
Sesquiterpenoids

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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 CB₂ 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 CB₂ knockout mice (Zimmer 2009)
- ? Utility in contact dermatitis (Karsak 2007)
- Decreased cocaine administration (Bahi 2014)
- β-Caryophyllene demonstrated larvicidal activity against vectors of malaria, dengue, and Japanese encephalitis (Govindarajan 2016).
- Broad additional pharmacology (Sharma 2016)
Caryophyllene oxide

- Sesquiterpenoid oxide
- The cannabis component by which sniffer dogs identify cannabis (Stahl 1973)
- Antifungal in onychomycosis comparable to ciclopiroxolamine and sulconazole (Yang et al. 1999). 8% CO→ onychomycosis cure in 15 days.
Humulene

- Very common in North American chemovars, sometimes predominant (Giese 2015)
- Inhibits fruit fly mating (Shelly 2015)
- Protected rat astrocytes from $\text{H}_2\text{O}_2$-induced cell death by 50%, and was concentrated 7-fold intracellularly (Elmann 2009).
Guaiol

- A bicyclic sesquiterpenoid alkene alcohol
- *Bulnesia sarmientoi* essential oil has been employed in aromatherapy to treat arthritis, rheumatoid arthritis and gout.
- Reported actions of the essential oil are: anti-inflammatory, anti-oxidant, anti-rheumatic, antiseptic, diaphoretic, diuretic, laxative.
- Park (2003) demonstrated weak 5-alpha reductase inhibitory effects, possibly helpful in benign prostatic hyperplasia, or male-pattern baldness
- Guaiol inhibited non-small cell lung cancer cells *in vitro*, and *in vivo* in nude mice as effectively as cisplatin at the same 8 mg/kg dose (Yang 2016)
- Guaiol showed contact toxicity for two moth species and efficacy as a fumigant for *Musca domestica* houseflies with LC50 of 16.9 µL/L (Liu 2013).
- Guaiol demonstrated bite-deterrence index (BDI) against pathogenic mosquitoes comparably to DEET (Ali 2015).
- Guaiol, was said to be a distinguishing factor in Afghan cannabis chemovars (Hillig 2004), with similar claim for “indica” chemovars (Hazekamp 2016).
Beta-Elemene

- A monocyclic sesquiterpenoid polyalkene

- Elemene injection approved in China since 1993 for treatment of cancer. However, a 2006 Cochrane-style review or 127 RCTs showed poor adherence to CONSORT recommendations and very low Jadad scale scoring (Peng 2006).

- A study in rats at 80 mg/kg IV (equivalent to 13 mg/kg in humans) good passage through the blood-brain barrier and attainment of high brain tissue levels, as well as good tumor inhibition and life extension (Wu 2009).

- A meta-analysis of studies in malignancy (Xu 2013) examined 38 clinical trials. Overall response rate of elemene with chemotherapy was favorable in lung cancer (p<0.00001), hepatocarcinoma (p=0.002), metastatic brain cancer (p=0.02), and leukemia (p=0.0004), but not in gastric carcinoma.

- Elemene increased cytotoxicity significantly in various cell lines over-expressing the ABCB1 transporter of paclitaxel, colchicine and vinblastine by inhibiting its efflux activity (Dong 2015). It also dose-dependently inhibited survival and proliferation of glioblastoma multiforme cell lines when combined with temozolomide or radiation (Liu 2015). In A549 human basal cells, elemene increased radiosensitivity (Zou 2015). Radiosensitivity of gastric cancer was also enhanced (Liu 2015). Elemene was the first drug reported to inhibit TOPO I and II simultaneously, as demonstrated in HepG-2 human hepatocarcinoma (Gong 2015). Elemene mediated multi-drug resistance or various genes in exosomes in MCF-7 human breast cancer cells, sensitizing them to docetaxel and adriamycin (Zhang 2015). In A109 esophageal carcinoma cells, elemene reduced proliferation, increase apoptosis, reduced invasiveness and mouse xenograft growth (Zhu 2015). Elemene was noted to inhibit cancer growth via multiple mechanisms of proliferative signaling suppression (Zhang 2016): MAPK and PI3K/Akt/mTOR pathways, upregulation of growth suppressors, promotion of apoptosis, diminishing invasion and metastasis, affecting cell immortality and reducing angiogenesis. While concentrations of elemene employed would likely never be attained with cannabis extracts, the distinct possibility of synergy or elemene with chemotherapeutic phytocannabinoids should certainly be explored.

- Elemene prevented human umbilical vein endothelial cell (HUVEC) damage by hydrogen peroxide in vitro, inhibited smooth muscle proliferation and migration, and neointima formation after vessel injury in rats (Wu 2011). In subsequent work (Liu 2015), elemene also decreased reactive oxygen species and mitogen-activated protein kinase signaling in HUVECs, and suggesting utility in atherosclerosis treatment.

- In a rat model of hepatic fibrosis, elemene downregulated plasma endotoxins, serum TNF-α and expression of CD14, the co-receptor for bacterial lipopolysaccharide detection (Liu 2011).

- Elemene 12.5-50 µg/ml inhibited osteogenic differentiation from cultured human hip joint capsule fibroblasts via inhibition of the BMP/SMADs pathway, suggesting its ability to reduce ectopic ossification in ankylosing spondylitis (Zhou 2015).

- Elemene 10-200 µg/ml also reduced viability and increased apoptosis of rheumatoid arthritis fibroblast-like synoviocytes via induction of ROS and p38 MAPK activation, implying therapeutic potential in that disorder (Zou 2016).
Cannabis Odds & Ends

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Friedelin

- The most prominent triterpenoid in cannabis, concentration in cannabis root, was calculated as 12.8 mg/kg (Slatkin 1971).
- Friedelin was weakly active (35 µM or above) against four cancer cell lines (Ee 2005).
- In adult Wistar albino rats, friedelin markedly reduced carrageenan-induced hind paw edema (Antonisamy 2011). Results of friedelin at 40 mg/kg dose were comparable to those of indomethacin 10 mg/kg. Doses of 2 or 4 mg markedly reduced rat ear edema after croton oil administration, inhibited peritoneal capillary permeability after acetic acid administration in a dose-related manner. Friedelin inhibited granuloma formation, inhibited paw swelling after Freund's adjuvant injection, and reduced abdominal constrictions and stretching after acetic acid injection.
- Friedelin showed reducing power in vitro, comparable to BHT and ascorbate, which was dose-related (Sunil 2013). In five in vitro antioxidant assays, the following results were noted at high concentrations: DPPH radical scavenging effect, hydroxyl radical scavenging, nitric oxide radical inhibition, superoxide radical, inhibition of lipid peroxidation. Friedelin 40 mg/kg pre-treatment reduced CCl₄-induced LFT elevations due to hepatic damage, comparable to silymarin extract of Silybum marianum (milk thistle). Friedelin 40 mg/kg pre-treatment before CCl₄ administration produced highly significant increases in superoxide dismutase, catalase and glutathione peroxidase levels (p<0.005) to normal values, comparable to silymarin.
- Demonstrated antimycobacterial activity against three non-pathogenic species at a minimum inhibitory concentration (MIC) of 800 µg/ml (Christopher 2014), and merited mention as a natural African anti-tuberculosis agent (Chinsembu 2016).
- Friedelin was also effective in protecting against ethanol-induced gastric ulceration in rats (Antonisamy 2015), comparable to the standard drug, omeprazole2%.
Epifriedelanol

- This triterpenoid molecule had a measured concentration in cannabis root of 21.3 mg/kg (Slatkin 1971).
- Utilized to assess adriamycin-induced cell senescence in human fibroblasts (HDF) and human umbilical vein endothelial cells (HUVEC) (Yang 2011), wherein epifriedelanol was especially active, and also decreased reactive oxygen species (ROS).
- “This compound [epifriedelanol] may be a promising candidate for developing dietary supplements or cosmetics to modulate tissue aging-associated diseases.” (p. 448)
(+)-Cannabisativine

- Cannabisativine was isolated from cannabis root (Slatkin 1975)(Lotter 1975) with calculated concentrations of 2.5mg/kg (Turner 1976) or 0.0004% (Mechoulam 1988).
- No pharmacological information available: “They are present in minuscule amounts and are presumably not relevant to any cannabis biological activity.” (Raphael Mechoulam, personal comm. to EBR 2013).
Anhydrocannabisativine was isolated from cannabis roots and leaves (Elsohly 1978), at calculated concentration 0.3 mg/kg, or 0.00046% (Mechoulam 1988).

No pharmacological information available: “They are present in miniscule amounts and are presumably not relevant to any cannabis biological activity.” (Raphael Mechoulam, personal comm. to EBR 2013).
Canniprene

- An isoprenylated bibenzyl unique to cannabis (up to 0.2% in leaves) (Allegrone 2017), that can be vaporized and is likely present in in smoke.

- **Potential anti-inflammatory demonstrated via inhibition of 5-LO (IC$_{50}$ 0.4 µM) and COX/mPGES pathway (IC$_{50}$ 10.1 µM).**

- Related compounds, cannabispiranol and cannabispirenone, were seeming inactive.

- While concentration did not correlate with phytocannabinoid content or developmental stage of the cannabis plant, it did have a reciprocal relationship with cannflavin A.
Hemp Seed Nutrition

- Possibly the single most nutritionally complete food on earth, and powerful anti-inflammatory
- Contains all essential amino acids
- 35% protein, as digestible edestin
- 35% oil, rich in essential fatty acids (EFA) in 3:1 ω6:ω3 ratio:
  - 75% linoleic acid (LA, ω-6)
  - 25% linolenic acid (LNA, ω-3)
  - 9% gamma-linolenic acid (GLA, ω-6) (Callaway 2004)
Cannflavin A • A flavone unique to cannabis (aerial parts)
• Very difficult to isolate and purify via crystallization from its isomer, cannflavin B.
• Inhibits PGE$_2$ thirty times more powerfully than ASA (Barrett 1986), and displays an anti-inflammatory potency intermediate to that of aspirin and dexamethasone.
• Noted to be produced in hemp seed sprouts of certain cultivars (Werz 2014). Cannflavin A (CFA) suppressed PGE$_2$, the primary mediator of inflammation, and directly inhibited mPGES-1 (at 1.8 µM), a target in inflammation and cancer. Cannflavin A did not significantly inhibit COX-1 nor COX-2. Dual inhibition of mPGES-1 and 5-LO is considered the ideal profile to treat inflammatory conditions with fewest side effects.
Cannabisin B

- Isolated from Chinese varieties (Chen 2012).
- Antioxidant activity against DPPH radical
- Showed prominent activity in inhibiting human LDL oxidation.
- In subsequent work (Chen 2013), cannabisin B produced antiproliferative effects in HepG2 human hepatic carcinoma cells (dose-dependently up to 500 µM).
**N-Trans-Caffeoyltyramine**

- Isolated from Chinese cannabis varieties (Chen 2012).
- Antioxidant activity against DPPH radical
- Showed prominent activity in inhibiting human LDL oxidation.
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