

Cannabis and Health

Module 1

Lecture 6: Deep Dive on Cannabinoid Pharmacology

Cannabinoid pharmacology

- Cannabinoids exist in the plant mainly as *carboxylic* precursors (THCa & CBDa)
- The carboxyl group is removed by light or heat while in storage or when combusted
- THCa and CBDa (with the carboxyl group) is synthesized within the *trichomes* present in the flowers and leaves of the female plant

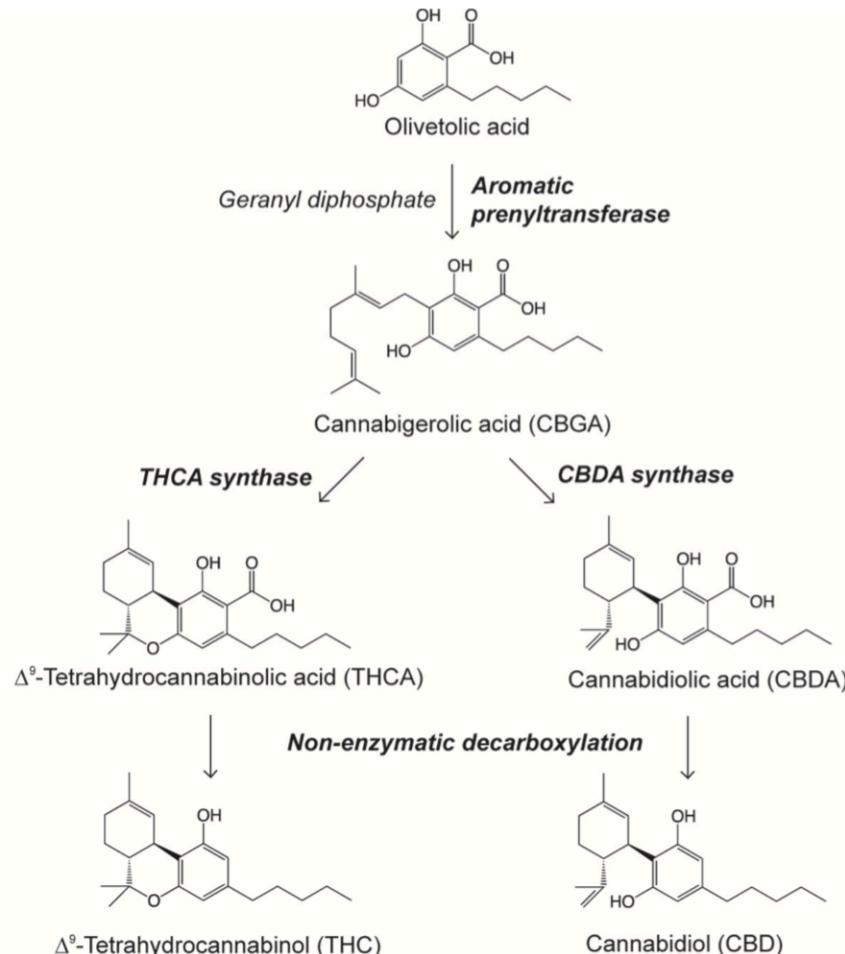


This means they have a carboxyl group attached, which makes them non-psychoactive



Cannabinoid Pharmacology

- THC and CBD share a common precursor, *olivetolic acid*

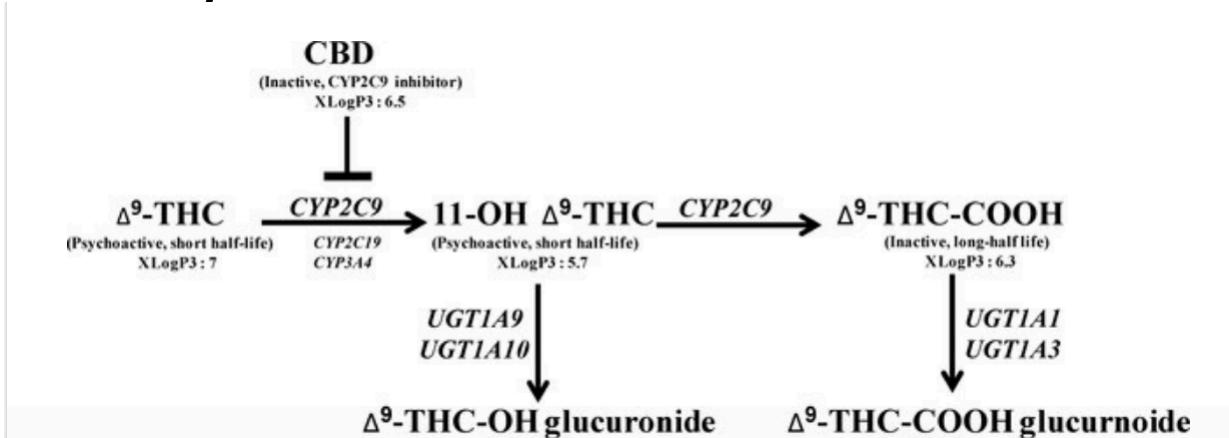


Converted to CBGa,
then THCa and CBDa,
and finally THC and CBD

FIGURE 2-1 Synthetic pathway of the main cannabinoids, Δ^9 -THC and CBD, from the common precursor, olivetol.

Cannabis Degradation and Metabolism in the Human Body

- THC is metabolized mainly to 11-OH-THC (11 Hydroxy THC)
 - 11-OH-THC is psychoactive
 - Further oxidized to THC-COOH (11-nor-9-carboxy-THC), which is inactive
- Metabolism occurs mainly in the liver by cytochrome P450 enzymes



From Jamwal et al., 2017

THCA, THC, CBDA, CBD Have Overlapping and Unique Effects

Citation: Nahler G, Jones TM (2018) Pure Cannabidiol versus Cannabidiol-Containing Extracts: Distinctly Different Multi-Target Modulators. *J Altern Complement Integr Med* 4: 048.

• Page 3 of 11 •

Cannabinoid	Targets	Effects (Examples)	Ref.
CBD	Agonist of 5-HT1A, TRPA1, TRPV1,2,3,4; PPARg, GPR3,6,18; antagonist of TRPM8; 5-HT3A, GPR55, adenosine transport protein; positive allosteric modulator of GABAA, GlyRs; inhibits n-AChR, NaV channels, LOX-5,-15; moderate inhibitor of FAAH	Anti-inflammatory, analgesic, anxiolytic, antidepressant; attenuates nausea, vomiting, motor and cognitive impairment; inhibits cancer cell growth	[14-24]
CBDA	Agonist of 5HT1A, TRPA1, TRPV1, TRPV4; antagonist of TRPM8; inhibitor of COX-2, NAAA	Anti-inflammatory, anxiolytic, antidepressant; attenuates nausea, vomiting, motor and cognitive impairment; antineoplastic	[16,25,26]
THC	Agonist of CB1, CB2, TRPA1, TRPV2, TRPV3, TRPV4; GPR18, PPARg; potentiates Glycine receptors (GlyRs); antagonist of TRPM8, 5-HT3A	Anti-inflammatory, anxiolytic, pro-apoptotic effects; analgesic (additive with kappa-Opioid-receptor agonists)	[16,27,28]
THCA	Weak binding to CB1, CB2; agonist of PPARg, TRPA1, TRPV2; antagonist of TRPM8; weak inhibitor of FAAH, MAGL, COX-1,-2	Anti-inflammatory, neuroprotective, pro-apoptotic effects	[29-31]
CBG	Agonist of TRPA1, TRPV1, TRPV2, TRPV4, PPARg; alpha2-adrenoceptor, Antagonist of 5-HT1A, TRPM8, CB1; inhibits NaV channels, COX-2	Antiemetic (may oppose effects of CBD), anti-inflammatory, antineoplastic, antidepressant; stimulates appetite, neuroprotective	[19,32-34]

Table 1: Main targets and effects of CBD, CBDA, THC, THCA.

CBD - Cannabidiol; CBDA - Cannabidiolic Acid; THC - delta-9-Tetrahydrocannabinol; THCA - Tetrahydrocannabinolic Acid; COX - Cyclooxygenase 1 or 2; LOX - Lipoxygenase; NAAA - N-Acylethanolamine Acid Amidase; NaV - Voltage gated Na⁺ (channels)

Reports of Widespread Actions

THC •
CBD ■

- ■ PROTECTS AGAINST CANCER
- ■ REDUCES NAUSEA
- ■ REDUCES PAIN
- CAUSES DROWSINESS
- ■ INCREASES APPETITE
- ■ ANTIDEPRESANT
- ■ RELIEVES SPASMS
- DECREASES SEIZURES
- REDUCES ANXIETY
- ■ ANTIMICROBIAL
- ANTIBACTERIAL
- ■ MUSCLE RELAXANT
- ■ PROTECTS NERVOUS SYSTEM
- ANTI-DIABETIC
- IMPROVES BLOOD CIRCULATION
- RELIEVES PSORIASIS
- ■ RELIEVES CROHN'S DISEASE
- ■ ANTI-INFLAMMATORY
- BONE STIMULANT
- RELIEVES RHEUMATOID ARTHRITIS
- ANTIOXIDANT
- ANTIPSYCHOTIC

Majority of these claims
lack conclusive evidence
in humans as we will see
in future modules !!!

The Health Benefits of Cannabidiol (CBD)

Slows Cancer Cell Growth

Research shows that cannabidiol works to slow and even stop cancer cells from spreading by turning off specific genes essential to the growth of cancerous tumours.



Treats Glaucoma

Cannabinoids decrease pressure in the eye, relieving the increased eye pressure associated with Glaucoma.



Decreases Parkinson's Tremors

Based on a study done in Israel, Parkinson's sufferers showed decreased tremors and pain while improving sleep function when using medical cannabis.



Helps with Hepatitis C Treatment

Medical cannabis users were way more likely to complete their Hepatitis C treatment (86%) compared to their non-cannabis using counterparts (29%).



Treats Crohn's Disease

Researchers found that cannabis improves gut health of Crohn's disease patients.



Improves Epileptic Seizures

Research from New York University shows that seizure sufferers who were resistant to pharmaceuticals responded positively to cannabidiol.



Keeps You Thin

Cardio isn't the only way to stay skinny. Cannabis users are significantly less likely to be obese compared to non-users.



Pain Relief

Those with chronic pain have found that using cannabis is more effective at reducing pain than taking Aspirin.



Reduces PTSD Symptomatology

Preliminary research shows that cannabis improves several PTSD-related symptoms including flashbacks, poor sleep, and agitation.



Asthma

Based on a study that looked at asthma sufferers over 20 years, cannabis actually improved pulmonary functioning.



Relieves Arthritis Symptoms

Arthritis sufferers reported pain reduction and improved sleep using a cannabinoid-based medication.



Anxiety Reduction

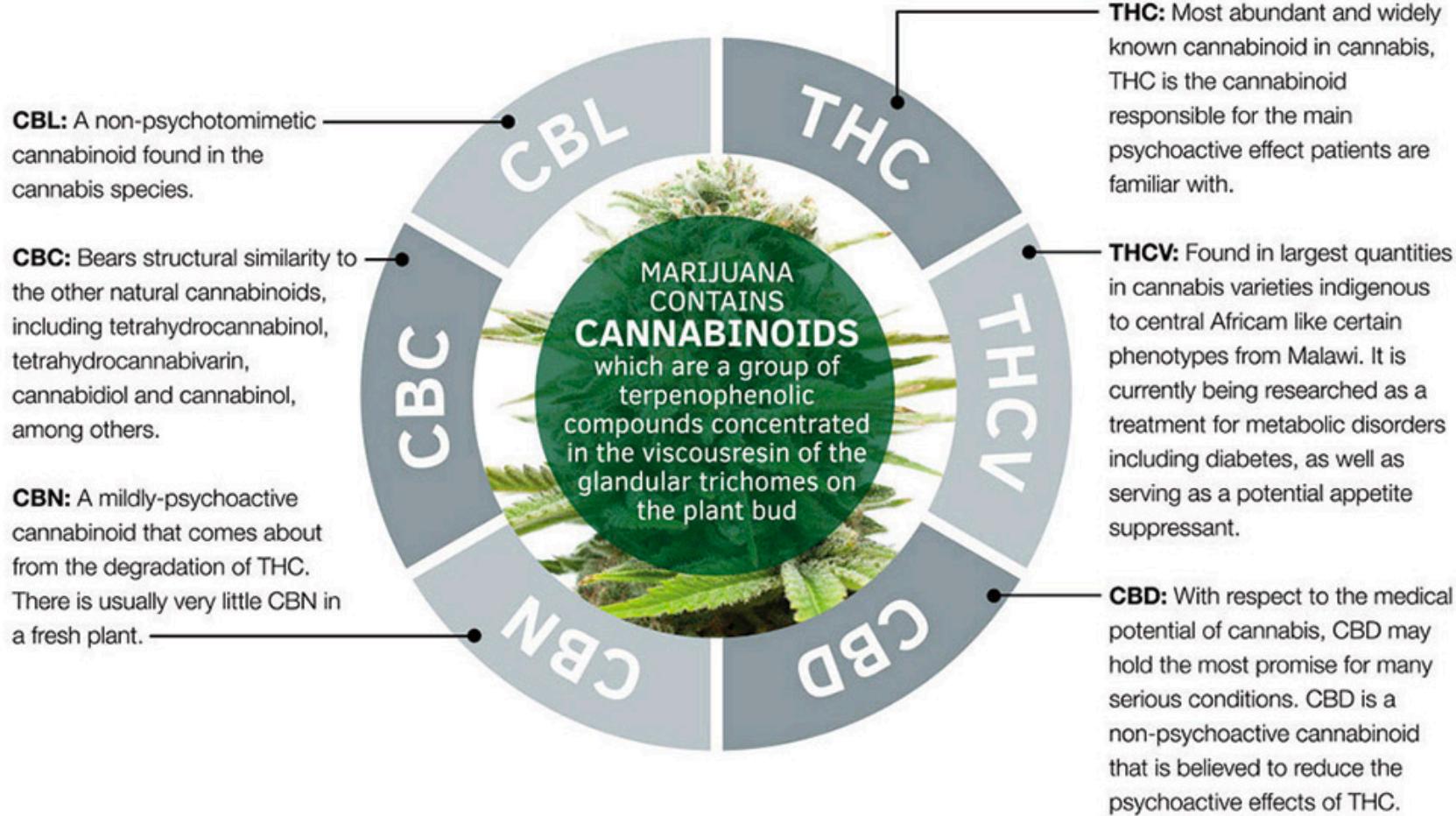
Cannabinoid use has been shown to decrease levels of anxiety, according to a Harvard study.



The Critical CBD Question

- **How can CBD possibly have such widespread effects?**
- Are people just responding to the placebo effect?
- Or could there be something about the pharmacology of CBD or other compounds (THC, CBG, CBD, terpenes) that come along with it that really could account for such diverse effects on the brain and body?

Other Major Cannabinoids



Other cannabinoids in our research (ng/ml)?

	High CBD	1:1 THC CBD	High THC	Concentrates
CBC	12.88 (3.15 – 31.32)	9.99 (0.00 – 73.3)	11.71 (1.37 – 28.1)	5.32 (0.00 – 35.77)
CBG	1.79 (0.00 – 4.07)	2.19 (0.00 – 22.2)	3.36 (0.00 – 11)	3.02 (0.00 – 19.05)
CBN	0.32 (0.00 – 1.81)	2.81 (0.00 – 22.0)	3.93 (0.00 – 13.80)	7.51 (0.00 – 39.98)
THCV	0.00 (0.00 – 0.00)	0.22 (0.00 – 3.02)	0.30 (0.00 – 1.72)	0.40 (0.00 – 11.53)

Themed Issue: Cannabinoids in Biology and Medicine, Part I

REVIEW

Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects

Ethan B Russo

GW Pharmaceuticals, Salisbury, Wiltshire, UK

Correspondence

Ethan Russo, MD, 20402 81st Avenue SW, Vashon, WA 98070, USA. E-mail:
ethanrusso@comcast.net

Keywords

cannabinoids; terpenoids;
essential oils; THC; CBD;
limonene; pinene; linalool;
caryophyllene; phytotherapy

Received

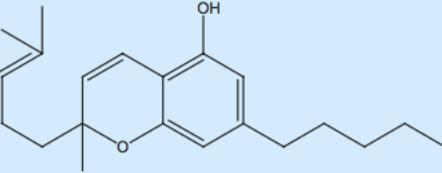
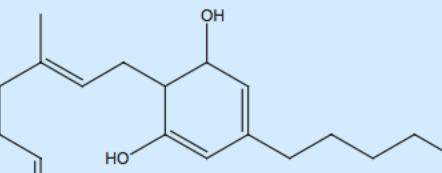
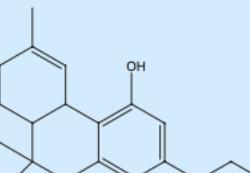
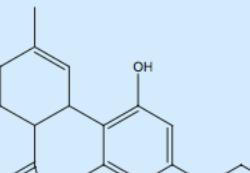
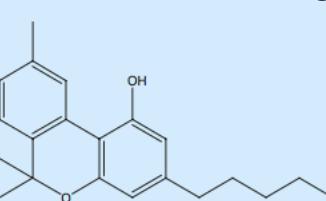
19 November 2010

Revised

29 December 2010

Accepted

12 January 2011

	CBC	Anti-inflammatory/analgesic (Davis and Hatoum, 1983) Antifungal (ElSohly <i>et al.</i> , 1982) AEA uptake inhibitor (De Petrocellis <i>et al.</i> , 2011) Antidepressant in rodent model (Deyo and Musty, 2003)	Various Caryophyllene oxide – Limonene
	CBG	TRPM8 antagonist prostate cancer (De Petrocellis <i>et al.</i> , 2011) GABA uptake inhibitor (Banerjee <i>et al.</i> , 1975) Anti-fungal (ElSohly <i>et al.</i> , 1982) Antidepressant rodent model (Musty and Deyo, 2006); and via 5-HT _{1A} antagonism (Cascio <i>et al.</i> , 2010) Analgesic, α-2 adrenergic blockade (Cascio <i>et al.</i> , 2010) ↓ keratinocytes in psoriasis (Wilkinson and Williamson, 2007) Effective versus MRSA (Appendino <i>et al.</i> , 2008) AI/anti-hyperalgesic (Bolognini <i>et al.</i> , 2010)	Cannabis terpenoids Phytol, linalool Caryophyllene oxide Limonene Various adjunctive role? Pinene Caryophyllene <i>et al.</i> . . .
	THCV	Treatment of metabolic syndrome (Cawthorne <i>et al.</i> , 2007)	–
	CBDV	Anticonvulsant (Hill <i>et al.</i> , 2010) Inhibits diacylglycerol lipase (De Petrocellis <i>et al.</i> , 2011)	Linalool –
	CBN	Anticonvulsant in hippocampus (Hill <i>et al.</i> , 2010) Sedative (Musty <i>et al.</i> , 1976) Effective versus MRSA (Appendino <i>et al.</i> , 2008) TRPV2 agonist for burns (Qin <i>et al.</i> , 2008) ↓ keratinocytes in psoriasis (Wilkinson and Williamson, 2007) ↓ breast cancer resistance protein (Holland <i>et al.</i> , 2008)	Linalool Nerolidol, myrcene Pinene Linalool adjunctive role? Limonene

Terpenes

- Many terpenes are present in cannabis
- Amount differs by strain
- Also present in other plants
- Many are biologically active
- Do they exacerbate or mitigate the effects of cannabinoids?
- Also known as the “Entourage Effect”

TERPENE	BENEFIT	AROMA	
	Pinene Also found in pine needles	Anti-inflammatory Anti-bacterial Bronchodilator Aids memory	Pine Earth
	Myrcene Also found in hops	Sedative Sleep aid Muscle relaxant	Flowers Pungent Earth
	Limonene Also found in citrus	Treats acid reflux Anti-anxiety Antidepressant	Citrus Fresh spice
	Terpinolene Also found in coriander	Analgesic Pain reduction Digestive aid Stomachic	Pine Herbal Anise Lime
	Linalool Also found in lavender	Anesthetic Anti-convulsive Analgesic Anti-anxiety	Flowers Lavender Citrus Fresh spice
	Terpineol Also found in mugwort	Calming aid Antibacterial Antiviral Immune system	Pleasant lilac Citrus Wood
	Caryophyllene Also found in black pepper	Anti-inflammatory Analgesic Protects cells lining Digestive tract	Citrus Spice

Terpenoid	Targets	Effects (Examples)	Ref.
α,β -Amyrin	Activates CB1 (more potent than d9-THC); inhibits hydrolysis of MAGL, ABHD6, -12 and 2-AG; prevents NF- κ B activation	Antinociceptive, anti-hyperglycemic, hypolipidemic; anti-inflammatory	[56-59]
Borneol	Activates TRPV3; inhibits NF- κ B; positive allosteric modulator of GABAA receptors	Neuroprotective; antibacterial; occurs in hemp in low concentrations	[60,61]
β -Caryo-phyllene	Selective CB2-agonist; PPAR γ , α -agonist; nAChR antagonist	Anti-inflammatory (comparable to dexamethasone), analgesic; antibiotic, antineoplastic; reduces intracellular triglyceride accumulation	[62-67]
α -Humulene (α -caryo-phyllene)	Prevents NF- κ B and activator protein 1 (AP-1) activation	Anti-inflammatory (comparable to dexamethasone), anti-nociceptive; antineoplastic; antibacterial, appetite suppressant, insecticidal	[67-69]
D-Limonene +	Prevents activation of NF- κ B	Anti-inflammatory; antineoplastic; anxiolytic, insect repellent	[7,66,70-72]
D-Linalool Linalool oxide	Agonist to PPAR α	Anticonvulsive, antinociceptive, sedating, local anesthetic effects; reduces plasma triglycerides	[37,65,73,74]
β -Myrcene +	Prevents activation of NF- κ B	Anti-inflammatory, analgesic, sedative, muscle relaxant, blocks hepatic carcinogenesis by aflatoxin	[37,40,66,70,75]
Nerolidol	Prevents activation of NF- κ B; modulates GABAA receptors	Antinociceptive; anti-inflammatory, anxiolytic; enhances skin penetration, antimalarial	[76]
α -Pinene +	(+)- α -pinene prevents activation of NF- κ B; more potent than (-)- α -Pinene	Anti-inflammatory; chondro-protective; acetylcholinesterase-inhibitor, bronchodilator, antifungal, insect repellent; antibacterial (against MRSA)	[7,37,39,43,66,71,75,77]
α -Terpineol	Inhibition of COX-2 (superior to aspirin)	Anti-inflammatory, promotes wound healing	[70,78]
Terpinolene (delta-terpinene) 0	Inhibits AKT-formation in leukemia cells	Antiproliferative, sedative, promotes sleep; antibacterial, antifungal, insect repellent	[79,80]

Table 2: Main targets and effects of selected terpenoids.

Summary

- THCa and CBDa have common precursor in CBDa
- THCa (non psychoactive) and CBDa become THC and CBD through decarboxylation after exposure to heat
- THC is further metabolized by enzymes in the liver to 11-OH-THC (11 Hydroxy THC) which is also psychoactive
- Presence of many other active cannabinoids and terpenes have led to the hypothesis that the diverse effects of cannabis are a result of the combined of cannabinoids and terpenes (entourage effect)