Cannabis 101:

What you need to know to answer your patients' questions and feel good about it!

Congress of Medical Excellence 2.0

American Osteopathic Society of Rheumatic Disease

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Faculty Disclosure

Faculty member Kenton Crowley discloses the following relationships:

Director of Research and Development, Silver State Trading, NV

Founder and CEO, Trokie California Inc, CA

Inventor, Trokie®

Learning Objectives

- Overview of cannabis and its constituents
- Review the most clinically important families of the CYP450 system that are impacted by phytocannabinoids.
- Review the different delivery methods for cannabis and their impact on onset and duration of affects.
- Review common side-effects of cannabis and how they relate to the route of administration.

Marijuana vs Hemp

- Both are *Cannabis sativa L.*
- Regulatory terms based on delta-9-tetrahydrocannabinol (THC) content
  - Marijuana: > 0.3mg/gm of THC in the dry weight of plant
    - Schedule 1 drug = No recognized medicinal value, highly addictive
  - Hemp: $\leq$ 0.3mg/gm of THC in the dry weight of plant
    - Amended Farm Bill of 2018
      - Agricultural commodity
      - Legal in states that have approved USDA programs
      - Federally legal by default as (program rolls out) in state approved programs

Cultivar vs Chemovar vs Strain

- **Cultivar** (strain) are phenotypically different plants named by the grower based on smell, appearance and physiological effects
  - Common terms (usually inaccurate):
    - **Sativa**: Taller plant, more energetic, “head high”
    - **Indica**: Shorter plant, more relaxing, “body high”
    - **Hybrid**: A mix of the two and >95% of the flower market
      - Varieties: Jack Herer, Blueberry, Cannatonic
- **Chemovar** are determined by terpene profile, cannabinoids, potency and quantity of standard biomolecules (i.e. lipids, waxes)
  - To better ensure reproducible cannabis experiences and effects

Hazekamp,A et al *Drug Testing and Analysis* 2012

Russo,E *Frontiers in Pharmacology* 2016

The Endocannabinoid System (ECS)

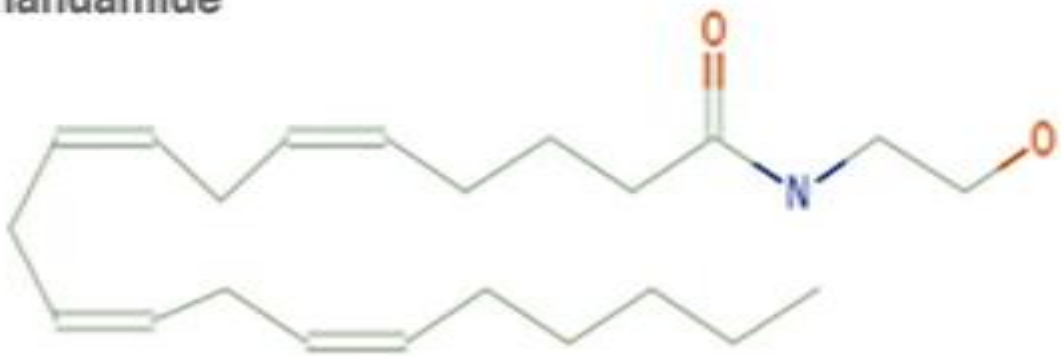
Endocannabinoids System (ECS)

- Establishing and maintaining health and homeostasis
  - *Front Behav Neurosci. 2012; 6: 9.*
  - Involved in Fertility, pregnancy, prenatal and postnatal development, appetite, pain-sensation, mood, memory, neuroprotection and inflammation
- Endocannabinoids play a role in:
  - neurotransmitter, immune system, and mitochondrial function; Have anti-proliferative, anti-inflammatory, and anti-metastatic effects *(Madia & Daeninck, 2016)*
- The main neurotransmitter associated with the “Runner's High”
  - *J.Exp. Biol.* ***215*** *(Pt 8): 1331–1336.*

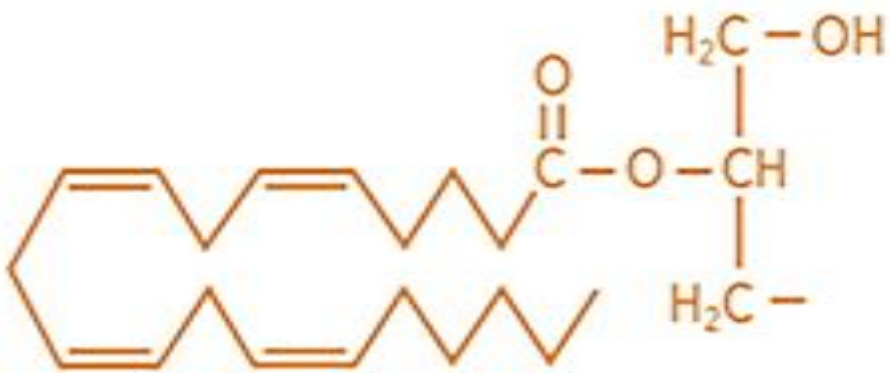
ENDOCANNABINOIDS

cannabis-like cannabinoids manufactured internally by the body

Anandamide



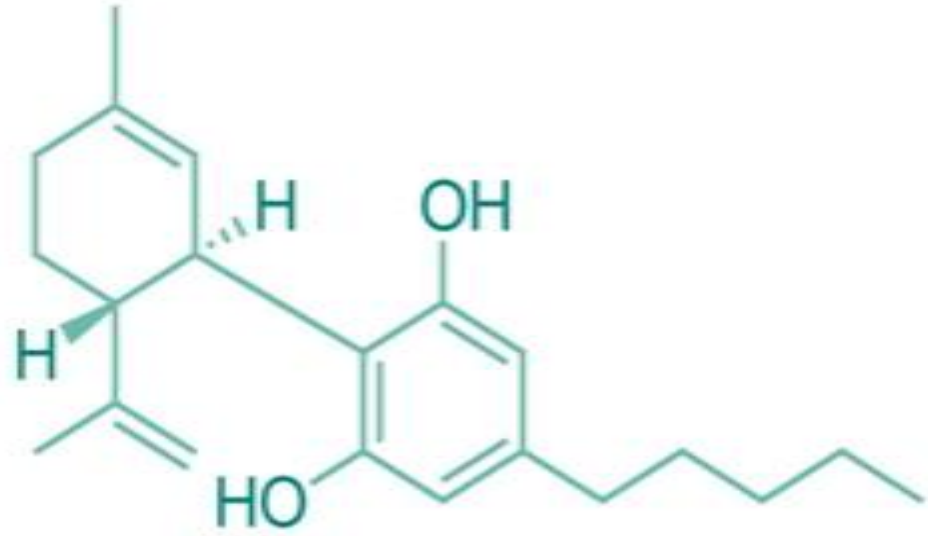
2-Arachidonoylglycerol (2-AG)



PHYTOCANNABINOIDS

cannabinoids found in cannabis plant and agricultural hemp

Cannabidiol (CBD)



The Human Endocannabinoid System

CBD, CBN and THC fit like a lock and key into existing human receptors. These receptors are part of the endocannabinoid system which impact physiological processes affecting pain modulation, memory, and appetite plus anti-inflammatory effects and other immune system responses. The endocannabinoid system comprises two types of receptors, CB1 and CB2, which serve distinct functions in human health and well-being.

THC

Tetrahydrocannabinol

CBD

Cannabidiol

CBN

Cannabinol

CB1 receptors are primarily found in the brain and central nervous system, and to a lesser extent in other tissues.

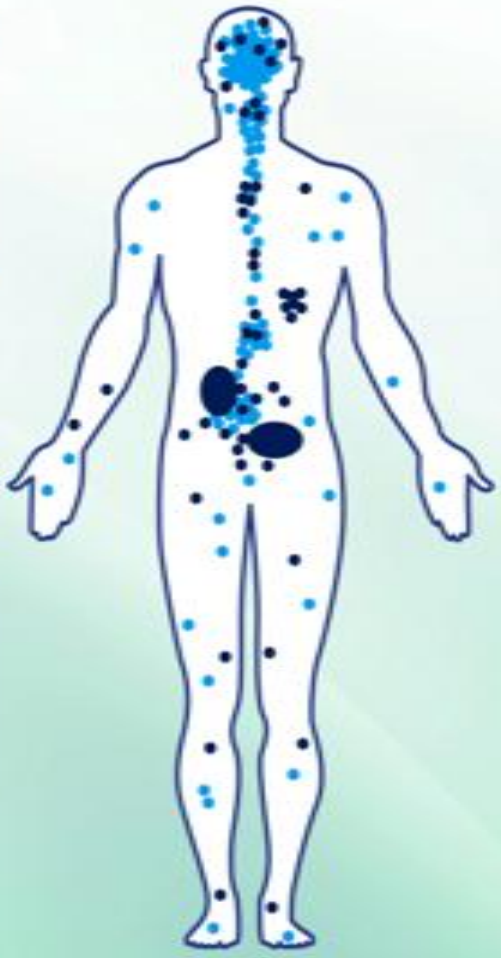
CB1

CBD does not directly "fit" CB1 or CB2 receptors but has powerful indirect effects still being studied.

CB2

CB2 receptors are mostly in the perepheral organs especially cells associated with the immune system.

Receptors are found on cell surfaces



source: www.the-human-solution.org

Cannabinoid receptor-independent mechanisms

- Serotonin receptors (5HT1A) R. de Mello Schier, A., et. al., 2014
- Vanilloid receptors (TRPV1) Devinsky O. et.al., 2104
- Orphan receptor (GPR55) Devinsky O. et.al., 2104
- Reuptake inhibition Deutch DG, 2016
- Allosteric modulation Bakas T, 2017; Khurana, L. et. al., 2017

Phytoconstituents of cannabis

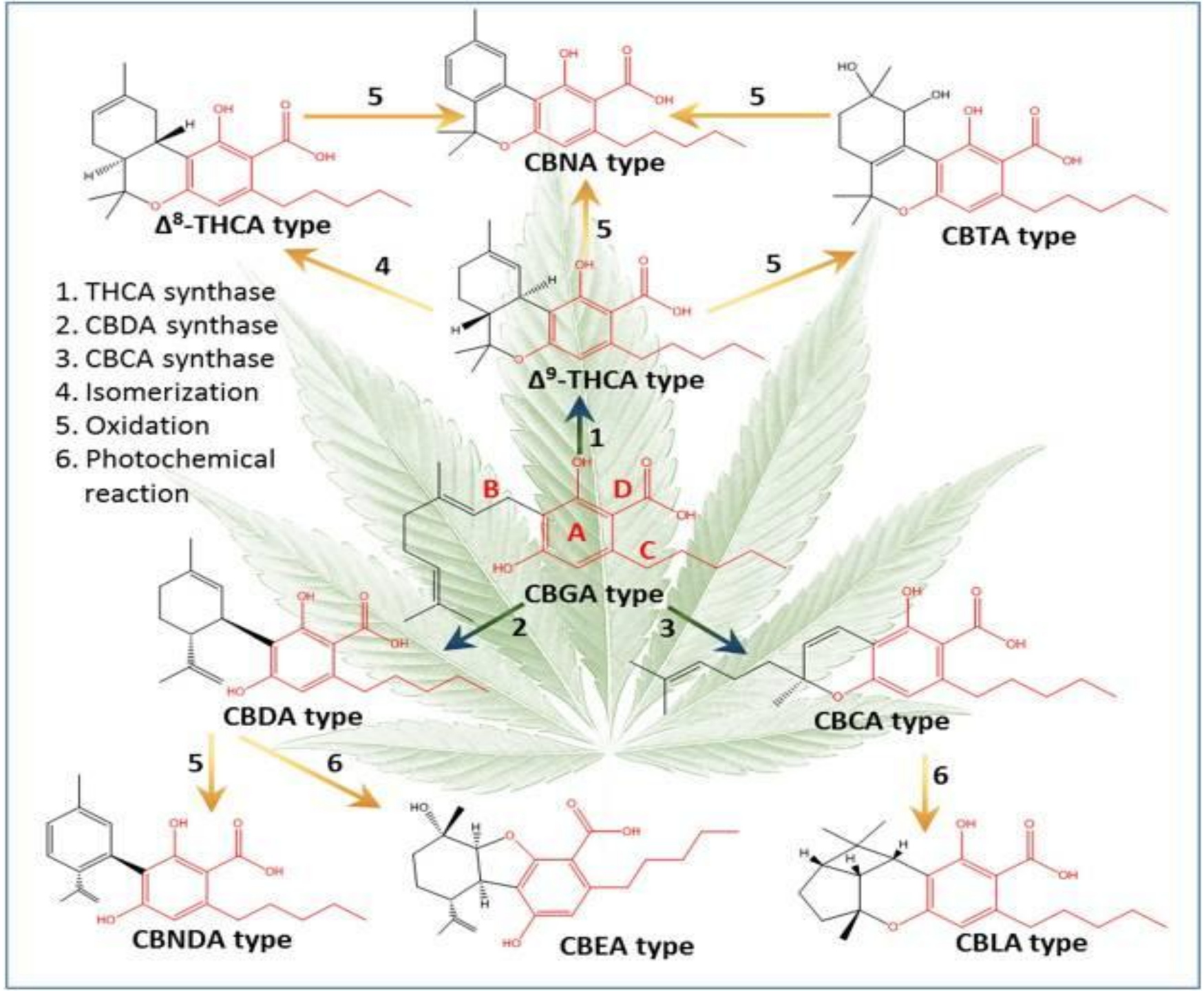


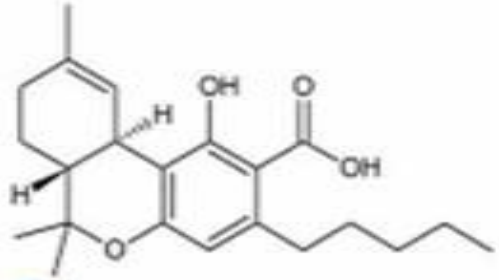
Diagram of phytocannabinoid acids and their metabolism

Acid forms:
CBGA Cannabigerolic Acid
CBDA Cannabidiolic Acid
THCA Tetrahydrocannabinolic acid
CBNA Cannabinolic acid

Neutral forms:
CBG (cannabigerol)
CBD (cannabidiol)
THC (tetrahydrocannabinol)
CBN (cannabinol)
CBC (cannabichromene)

Sci Rep. 2018; 8: 14280.

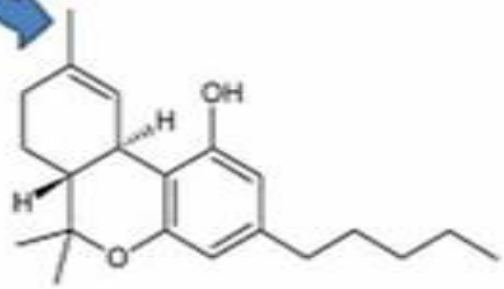
Cannabis flower



delta-9-tetrahydrocannabinolic acid

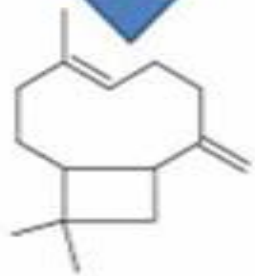
decarboxylation

Anti-TNF-α
Anticonvulsant
Antineoplastic
PPARγ agonist



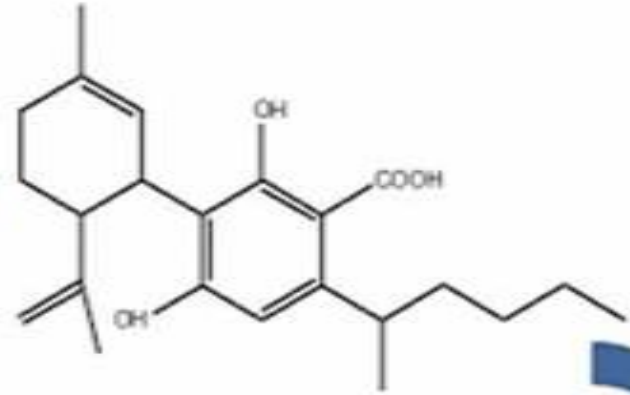
delta-9-tetrahydrocannabinol

Neuroprotective
Anticonvulsant
Muscle relaxant
Pro-microbiome



beta-caryophyllene

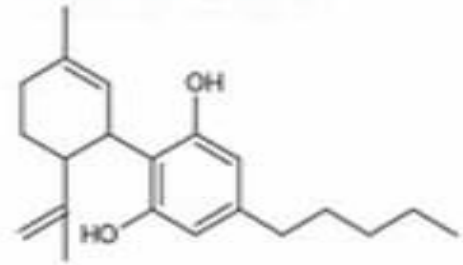
CB_2 agonist
Anti-inflammatory



cannabidiolic acid

$5\text{-}HT_{1A}$ agonist
Anti-emetic
Anticonvulsant
Antineoplastic?

decarboxylation

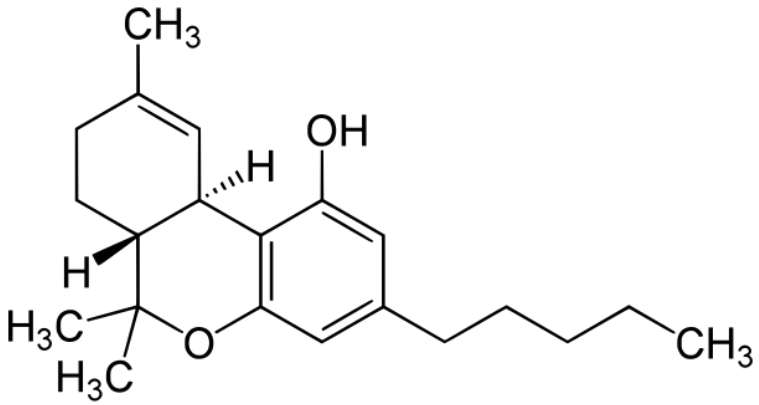


cannabidiol

Neuroprotective antioxidant
Anticonvulsant
Antineoplastic
Anti-anxiety/anti-psychotic
Antibiotic/anti-acne
PPARγ agonist

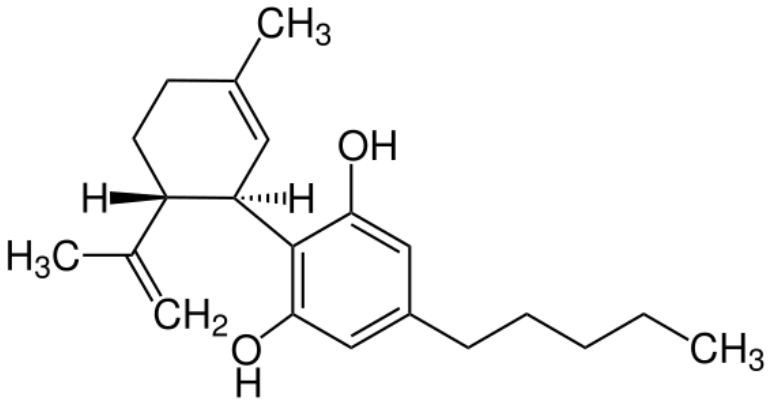
Main phytocannabinoids: THC and CBD

THC



- Partial agonist of type-1 and type-2 cannabinoid receptors (CB1 & CB2, respectively).
- Activation of central CB1 is responsible for the intoxicating (psychoactive) effects of THC.
- Reported effects: analgesic, anti-inflammatory, appetite stimulant, sedating, anti-emetic, antitumor, etc.

CBD



- Allosteric modulator of CB1 & CB2.
- Inhibitor of FAAH activity (in vitro).
- Serotonin 5-HT1A receptor and vanilloid TRPV1 receptor agonist.
- Inhibits adenosine deactivation.
- Reported effects: antioxidant, anti-inflammatory, anxiolytic, antiepileptic, antipsychotic etc.

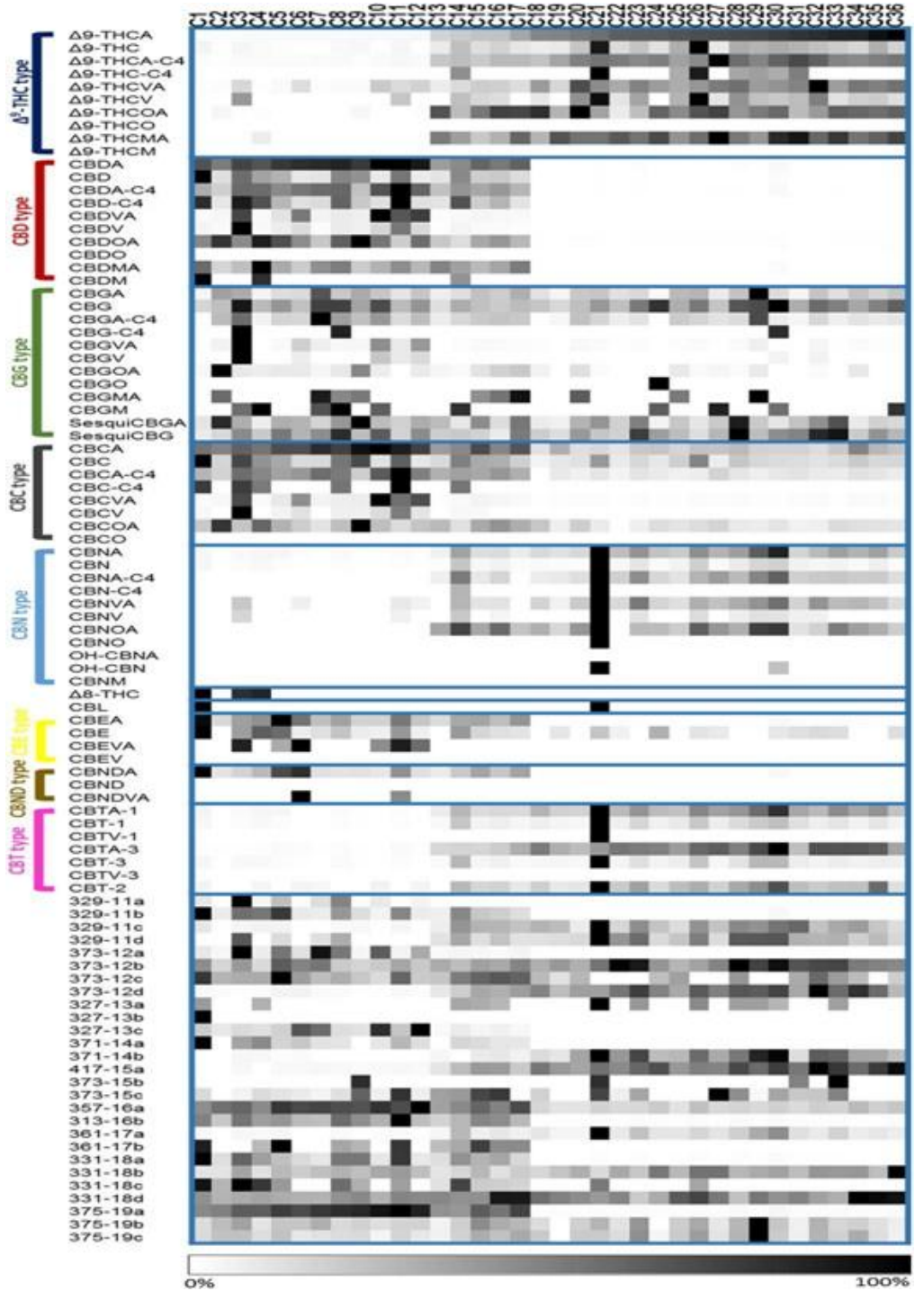
Sci Rep. 2018; 8: 14280.

Published online 2018 Sep 24. doi: 10.1038/s41598-018-32651-4

A new ESI-LC/MS approach for comprehensive metabolic profiling of phytocannabinoids in *Cannabis*

Paula Berman,1 Kate Futoran,1 Gil M. Lewitus,1 Dzmitry Mukha,1 Maya Benami,1 Tomer Shlomi,1,2 and David Meiri1

- 10 Δ^9-THC type
- 10 CBD type
- 12 CBG type
- 8 CBC type
- 11 CBN type
- 1 Δ^8-THC type
- 3 CBND type
- 7 CBT type



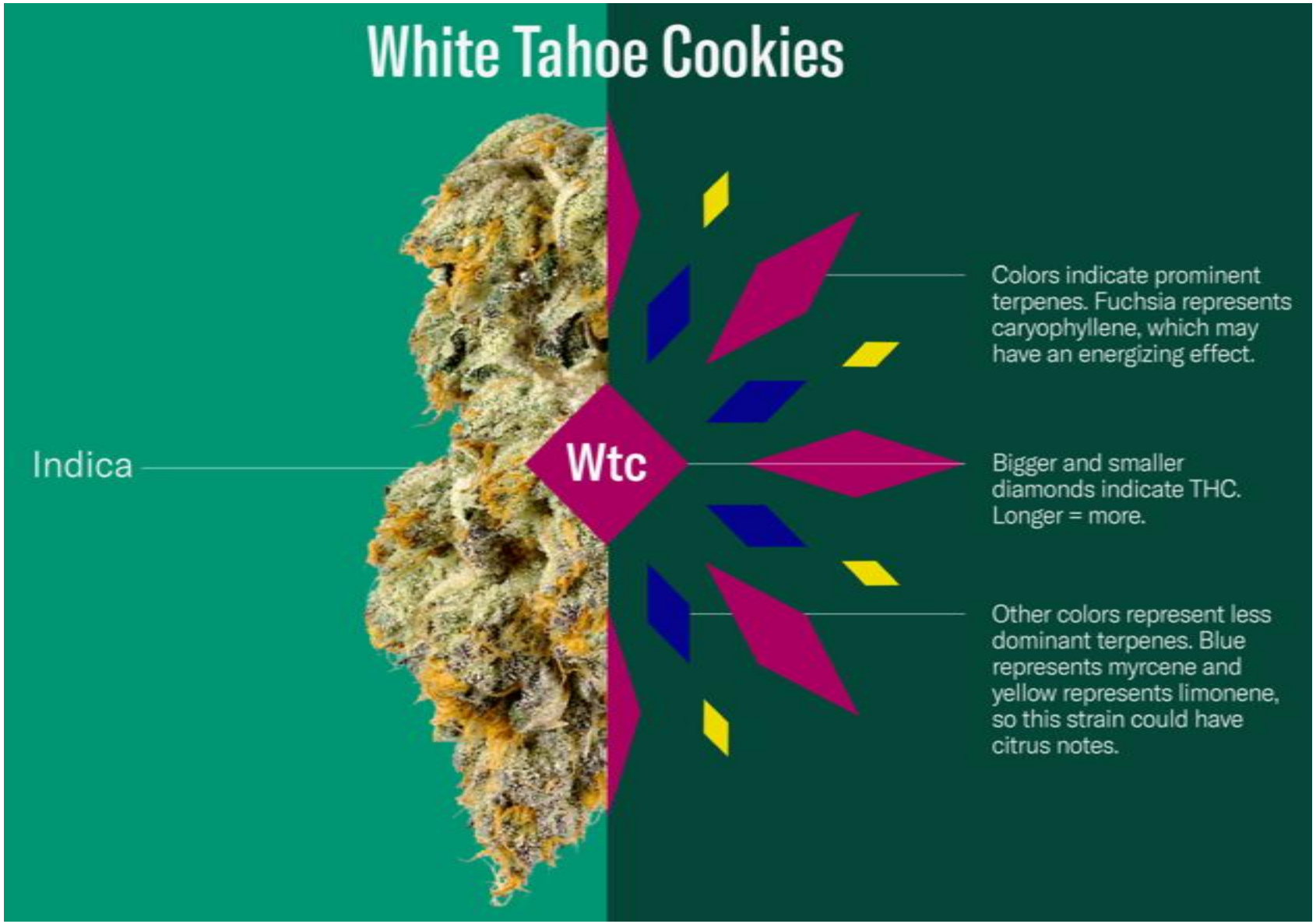
Terpene's: Aromatic substances that gives plants there unique scents and flavors

Three Catagories

Cannabis typically possess up to 200 terpenes

Possess their own individual effects and many times dominate the subjective experience of cannabis

Category	Compound	Industrial use
Monoterpenes [136]	Borneol	Cosmetics, household cleaners
	Camphene	Fragrances, pharmaceuticals, plasticizers, repellents, explosives
	D-3-carene	Repellents, manufacture of menthol, pesticides
	Carvacrol	Pharmaceutical
	Carveol	Fragrances, cosmetics, household cleaners, detergents
	p- cymene	Pharmaceuticals, repellents, disinfectants, solvents, flavorings
	Limonene	Fragrances, solvents, cleaning agents, flavorings, insect attractants, perfume industry
	Geranyl Linalool	Perfume industry, cosmetics, household cleaners, pharmaceutical
	Myrcene	Perfume industry, pharmaceutical
	Phellandrene	Perfume industry
	α-pinene	Fragrances, repellents, plasticizers, solvents, perfumery, insecticides
	β-pinene	Pharmaceuticals, fragrances, repellents, plasticizers, solvents, perfumery, insecticides
	α-terpineol	Fragrances, cosmetics, household cleaners, detergents, repellents, perfumery
	Toxaphene	Pesticides
Diterpenes [142]	Abietic acid	Paints, varnishes, lacquers, pharmaceuticals
	Dehydroabietic acid	Pharmaceuticals
	Geranylgeraniol	Potential antibacterial agent
	Isopimaric acid	Paper industry, pharmaceuticals
	Levopimaric acid	Paper industry
Sesquiterpenes [143]	Aromadendrene [144]	Potential antibacterial agent, food industry
	Bisabolene	Food additive, biofuel industry
	β-Caryopphyllene	Cosmetics, biofuels, perfume industry, food safety
	Farnesene	Insect repellent, chemical industry
	Germacrene	Food industry
	Longifolene	Chemical industry
	Isolongifolene	Fragrance, pharmaceutical



Decent resource on the internet for information on cannabis

Leafly.com

Find your color

The colors: terpenes

Calming ⟷ Energizing

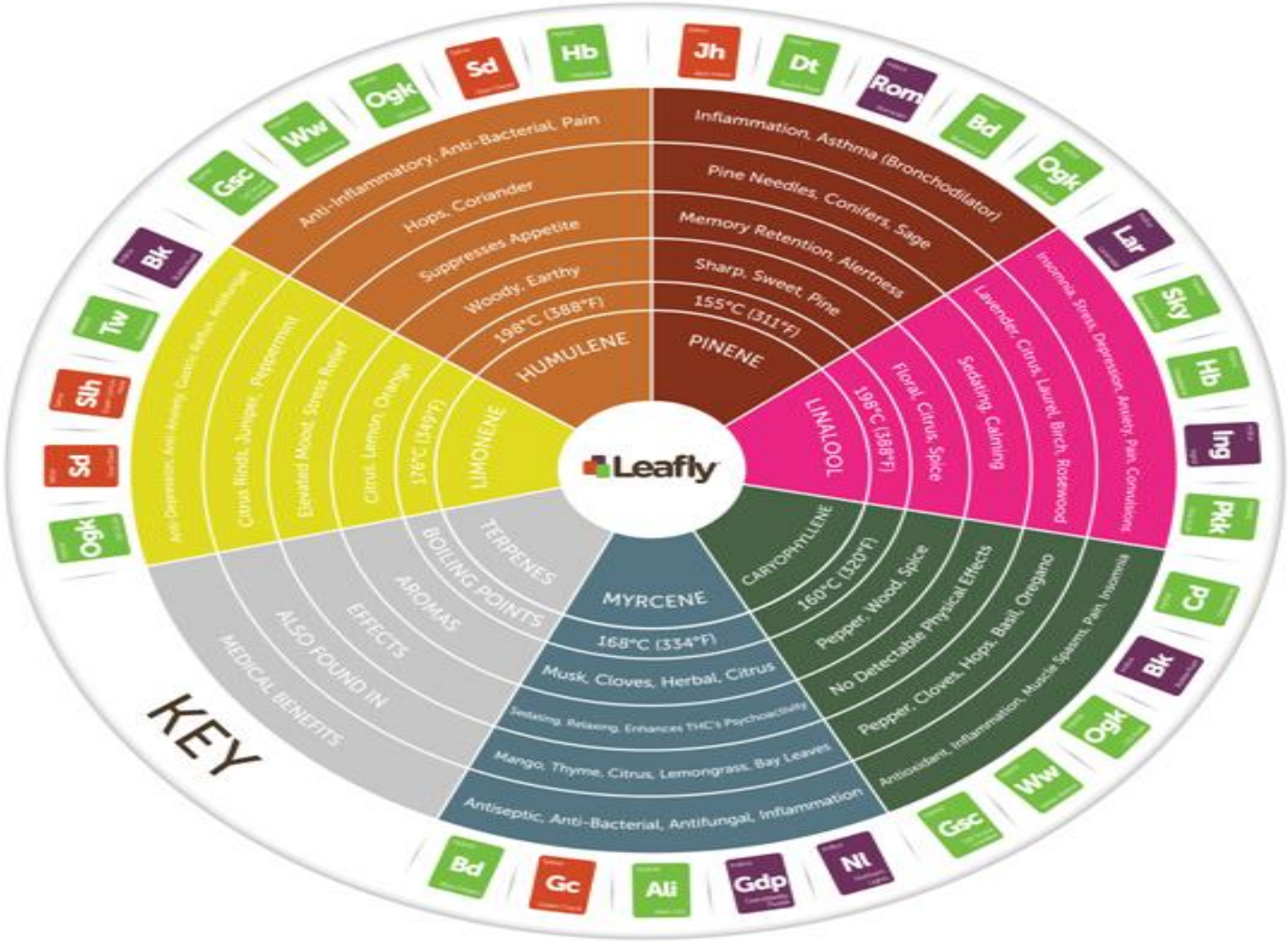
Myrcene *Earthy*
Also found in hops, mango, and lemongrass.

Pinene *Pine*
Found in pine needles, rosemary, basil, dill.

Caryophyllene *Pepper*
Found in black pepper, cloves, and cinnamon.

Limonene *Citrus*
Also found in fruit rinds, rosemary, juniper, peppermint.

Terpinolene *Fruity*
Also found in nutmeg, tea tree, cumin, and lilacs.



References
http://steephill.com/resources/cannabinoid-and-terpenoid-reference-guide/
http://sclabs.com/learn/terpenes.html

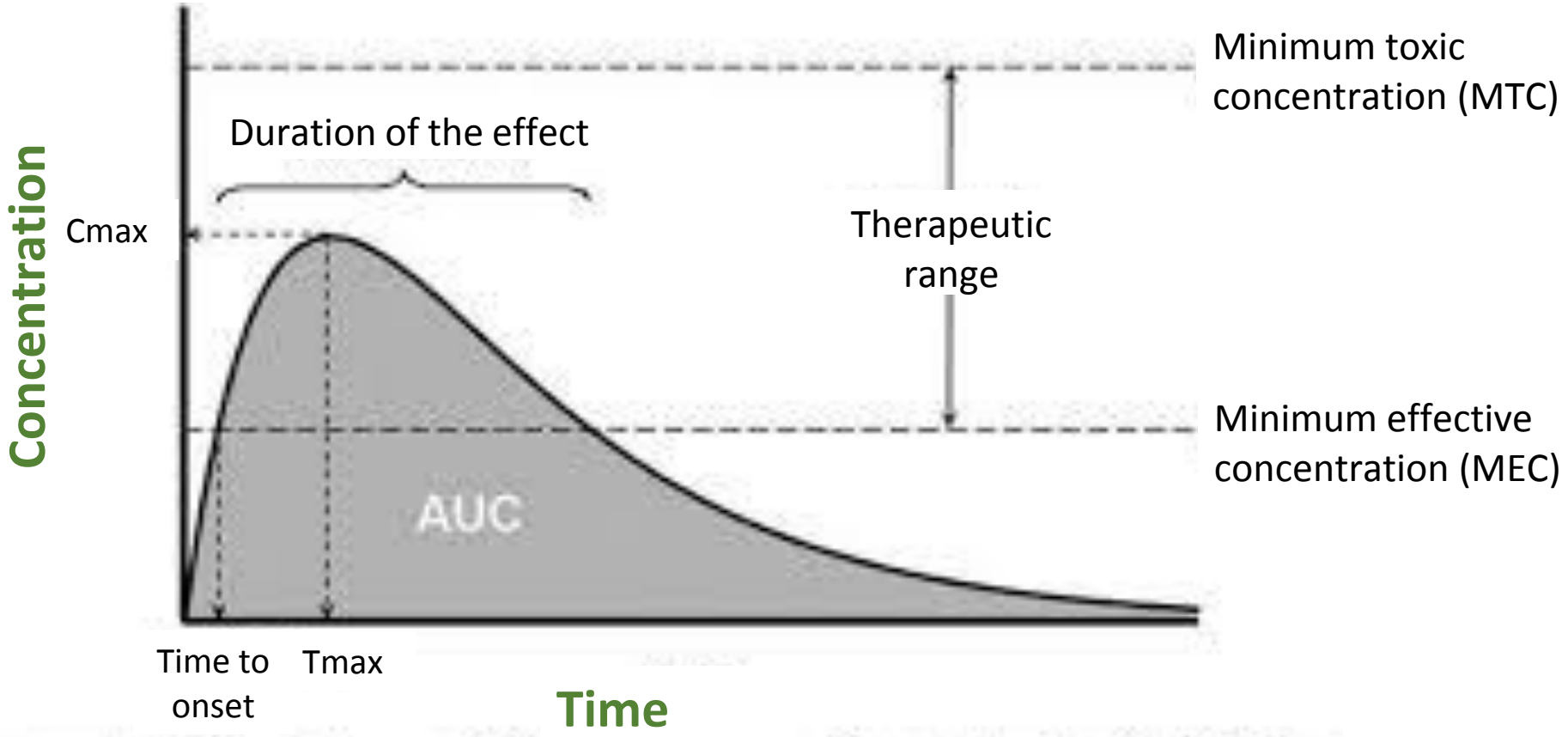
www.leafly.com
Information Wheel

Good resource for general information

Key:
Terpenes
Boiling points
Aromas
Effects
Also found in
Medical benefits
Associated cultivar and varital

Pharmacokinetics of Cannabinoids and Terpenes

Basic pharmacokinetic parameters



Cannabis pharmacokinetics fit in this model but many therapeutic endpoints do not (biphasic)

Inhalation: most common route of administration and published route

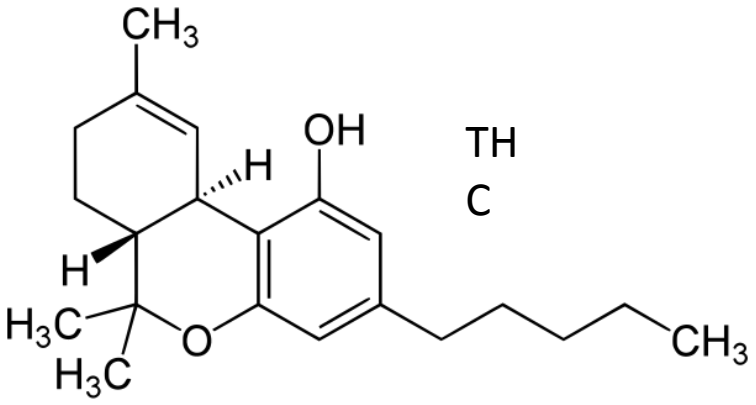
- **Smoked cannabis (Pérez-Reyes, 1990)**

- Traditionally preferred route (NIDA continues to distribute joints to patients).
- Bioavailability of THC depends on the way of smoking, high variability.
- Rapid route of administration (Tmax for THC is 5-9 minutes)
- Allows the experienced user to better **titrate** the doses by taking more of less hits.

Content of THC (%)	n	Cmax THC ng/mL ± SD	Range THC ng/mL
1.00	6	90.4 ± 20.2	45.6-187.8
1.32	6	100.0 ± 10.1	62.8-125.3
1.97	6	119.8 ± 10.6	44.5-180.9
2.40	18	63.0 ± 8.6	11.7-137.0
2.54	6	162.6 ± 18.7	107.4-204.7
4.84	12	124.2 ± 16.2	44.8-218.0

Cannabinoid-based pharmaceutical drugs

- **Marinol (dronabinol, synthetic THC)**



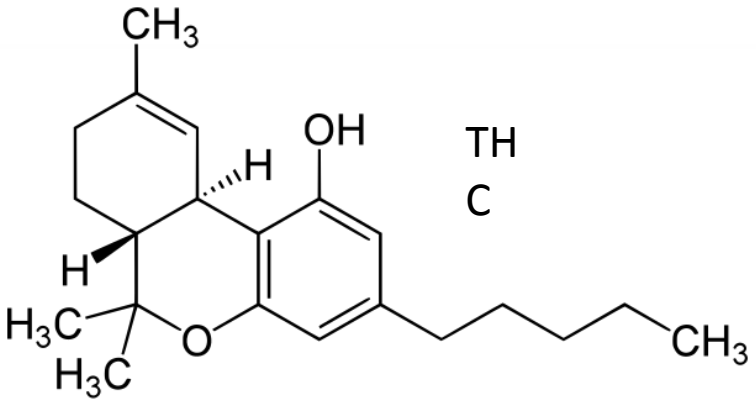
THC

- Soft-gel caps containing 2.5, 5, and 10 mg.
- Excipients: iron oxide, gelatin, glycerin, sesame oil, and titanium dioxide.
- High inter-individual variability.
- 90 to 95% is absorbed after single oral dose (only 10-20% gets to the bloodstream).
- High apparent volume of distribution (10 L/kg) and plasma protein binding is 97%.

Mean (SD) PK values for THC			
BID dose	Cmax ng/mL	Tmax (range), h	AUC (0-12) ng*h/mL
2.5 mg	1.32 (0.62)	1.00 (0.50-4.00)	2.88 (1.57)
5 mg	2.96 (1.81)	2.50 (0.50-4.00)	6.52 (1.85)
10 mg	7.88 (4.54)	1.50 (0.50-3.50)	15.2 (5.52)

Cannabinoid-based pharmaceutical drugs

- **Syndros (dronabinol, synthetic THC)**

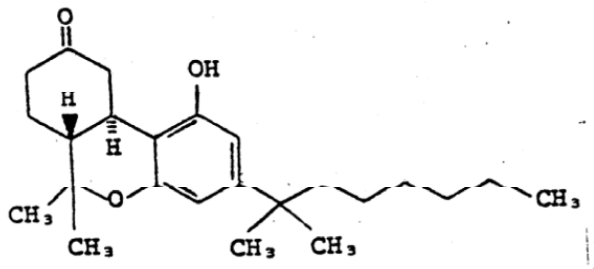


THC

- Oral solution (30 mL with syringe and adapter).
- 5 mg/mL of THC
- 50% w/w of ethanol; 5.5% w/w of propylene glycol.
- Reduces interindividual variability.
- Dose selection needs to be personalized.
- Intake with 200-250 mL of water.
- Indications:
  - Anorexia in AIDS wasting syndrome.
  - Chemotherapy-related nausea and vomiting.

Cannabinoid-based pharmaceutical drugs

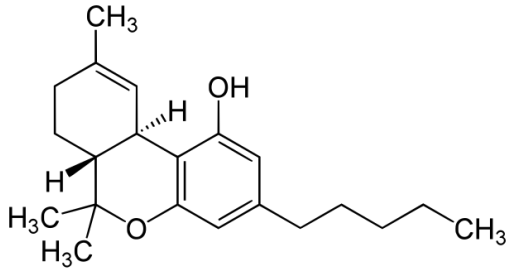
- **Cesamet (Nabilone, synthetic THC analog)**

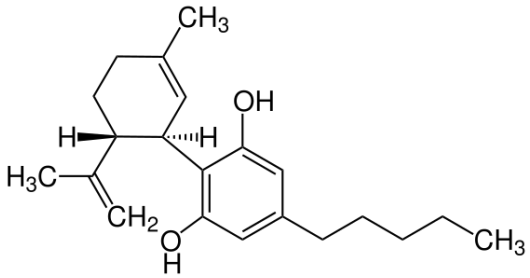


- Hard caps containing 1 mg (2.7 µmol) of nabilone.
- Excipients: povidone, corn starch, gelatin, and titanium dioxide.
- After 2 mg ingestion, Cmax=2ng/mL & $T_{1/2}$=2h approx.
- High apparent volume of distribution (12.5 L/kg)
- 90 to 95% is absorbed after single oral dose (only 10-20% gets to the bloodstream). Not affected by fasting.
- Approved for chemotherapy-related nausea and vomiting.
- Included on the schedule II of controlled substances.
- Adverse effects: somnolence, dizziness and euphoria.
- Maximum recommended dose is 6 mg (2 mg TID)

Cannabinoid-based pharmaceutical drugs

- **Sativex/Nabiximols (THC and CBD extracted from cannabis)**





- Sublingual spray, 2.7 mg THC & 2.5 mg CBD per spray.
- Excipients: ethanol, propylene glycol and peppermint oil.
- Approved for spasticity in MS and severe cancer pain.

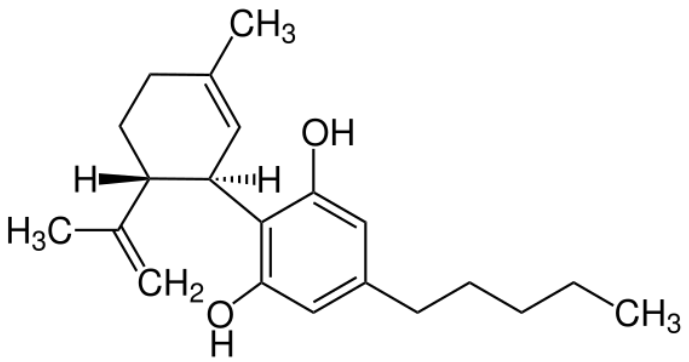
Mean (SD) of PK values for THC			
BID dose	Cmax ng/mL	Tmax (range), h	AUC (0-24) ng*h/mL
2 sprays	1.48 (0.53)	1.00 (0.75-1.50)	3.45 (1.78)
4 sprays	3.98 (2.28)	1.50 (0.75-2.00)	12.22 (7.14)
8 sprays	5.40 (2.41)	1.00 (0.75-1.50)	23.00 (18.76)

Mean (SD) of PK values for CBD			
BID dose	Cmax ng/mL	Tmax (range), h	AUC (0-24) ng*h/mL
2 sprays	0.39 (0.08)	1.00 (0.75-1.50)	1.54 (0.38)
4 sprays	1.15 (0.74)	1.39 (0.75-2.25)	5.02 (3.33)
8 sprays	2.17 (1.23)	1.00 (0.75-1.75)	10.37 (8.71)

A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray. Stott et al., 2013.

Cannabinoid-based pharmaceutical drugs

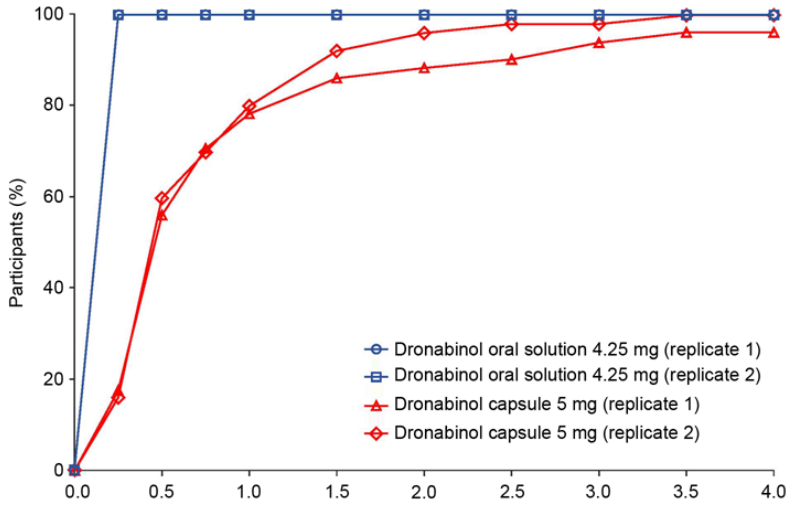
- **Epidiolex (CBD extracted from cannabis)**



- Transparent, colorless oral CBD solution (100mg/mL).
- Excipients: anhydrous ethanol, sesame oil, strawberry flavor and sucralose.
- Unknown pharmacological mechanism. Probably NOT mediated by cannabinoid receptors.
- Tmax=2.5-5h
- Administration with fatty meals may cause a 5-fold increase in Cmax and a 4-fold increase in AUC.
- Approved by FDA for refractory infant epilepsy (LG & DS)
- Weekly dose escalation: 5, 10 & 20 mg/kg/day
- Adverse effects: liver damage, somnolence, suicidal thoughts.

Cannabis therapeutics and routes of administration

- **Switch in formulation: Marinol vs Syndros (Parikh et al., 2016)**



THC detection in plasma after 15 min	<25 %	100 %
Mean Cmax	2.2-2.6 ng/mL	1.8-2.1 ng/mL
Intraindividual variability	53.8 %	66.3 %
Mean AUC	3.8-4.3 h x ng/mL	3.7-3.9 h x ng/mL
Intraindividual variability	36.8 %	13.5 %

Pharmacokinetics of Terpenes

Kohlert C, et al 2000: Review of published data in humans and animals

- More than 3000 compounds have been described, limited studies on most
- Clinical efficacy of essential oils, well established *in vivo*:
  - COPD, acute bronchitis, IBS, non-ulcer dyspepsia, tension-type headache
- Pharmacokinetic data available is very limited and few terpenes/terpenoids studied:
  - Biphasic elimination, short distribution and elimination half life (minutes to hours)
  - Skin is not a barrier to dermal application with only slightly longer times compared to IV
  - Sex has a significant impact (SQ fat an important factor); female elimination $t_{1/2}$ Double
  - Elimination pathways include pulmonary, renal and depend on route of admin and dose
    - phase-II elimination manly glucuronidation or exhaled as CO2
- Analytical methodology will be a rate limiting step to quality, reproducible data which is needed for therapeutic efficacy and safety.

Drug-Drug Interactions

Cannabis – Drug Interactions: CYP450

- Cytochrome P450 Enzymes (Phase I elimination)
  - More than 60% of prescription medications are metabolized by CYP450
  - All phytocannabinoids inhibit certain CYP450 enzymes
    - CYP2C, CYP2D and CYP3A families
  - CBD is the strongest inhibitor of all the phytocannabinoids studied to date
  - Most studies show little clinical impact when using normal therapeutic dosing of cannabinoids - in vitro work: 10 to 400 fold supratherapeutic concentrations used

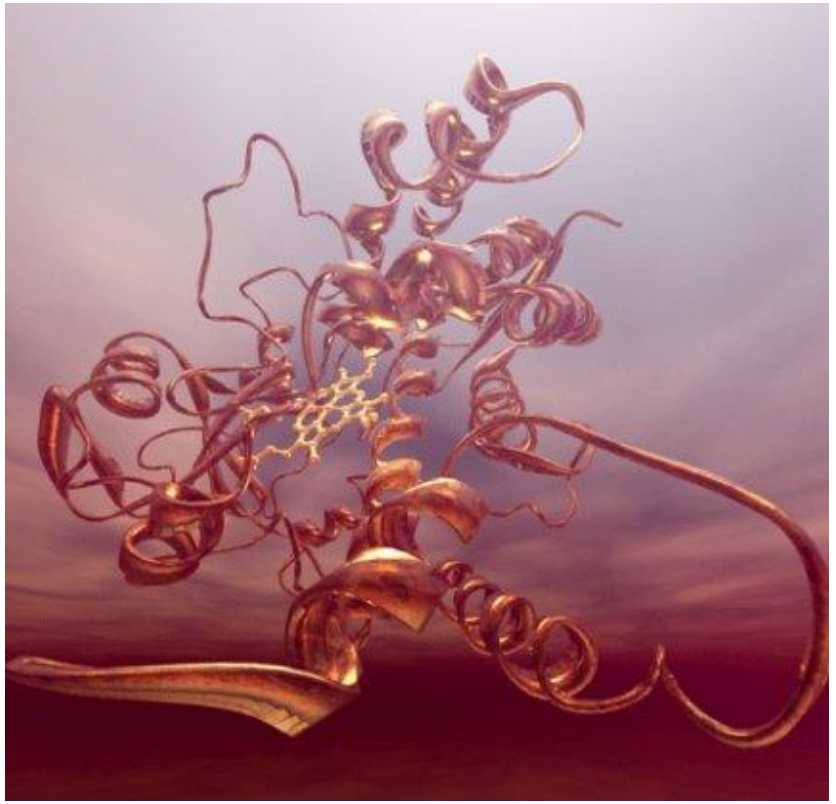


Photo credit: Scientific Images

Interaction between warfarin and cannabis

Damkier P1,2, Lassen D3, Christensen MMH1,2,4, Madsen KG5,6, Hellfritzsch M1,6, Pottegård A6.

Basic Clin Pharmacol Toxicol. 2019 Jan;124(1):28-31. doi: 10.1111/bcpt.13152. Epub 2018 Nov 6.

Delta-9-tetrahydrocannabinol (THC), the main psychoactive cannabinoid in cannabis, may inhibit the cytochrome P450 enzyme CYP2C9. Consequently, cannabis use might infer a risk of drug-drug interaction with substrates for this enzyme, which includes drugs known to have a narrow therapeutic window. In this study, we describe a case report of a 27-year-old man treated with warfarin due to mechanical heart valve replacement who presented with elevated international normalized ratio (INR) value (INR = 4.6) following recreational cannabis use. We conducted a review of the available literature, using the PubMed and EMBASE databases while following PRISMA guidelines. Following screening of 85 articles, three eligible articles were identified, including one in vitro study and two case reports. The in vitro study indicated that THC inhibits the CYP2C9-mediated metabolism of warfarin. One case study reported of a man who on two occasions of increased marijuana use experienced INR values above 10 as well as bleeding. The other case study reported of a patient who initiated treatment with a liquid formulation of cannabidiol for the management of epilepsy, ultimately necessitating a 30% reduction in warfarin dose to maintain therapeutic INR values. The available, although sparse, data suggest that use of cannabinoids increases INR values in patients receiving warfarin. Until further data are available, we suggest patients receiving warfarin be warned against cannabis use.

Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy

Geffrey, A. L., Pollack, S. F., Bruno, P. L. and Thiele, E. A. (2015), Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia, 56: 1246-1251. doi:10.1111/epi.13060

Under an expanded access investigational new drug (IND) trial, cannabidiol (CBD) is being studied as a possible adjuvant treatment of refractory epilepsy in children. Of the 25 subjects in the trial, 13 were being treated with clobazam (CLB). Because CLB and CBD are both metabolized in the cytochrome P450 (CYP) pathway, we predicted a drug–drug interaction, which we evaluate in this article.

Thirteen subjects with refractory epilepsy concomitantly taking CLB and CBD under IND 119876 were included in this study. Demographic information was collected for each subject including age, sex, and etiology of seizures, as well as concomitant antiepileptic drugs (AEDs). CLB, *N*-desmethylclobazam (norclobazam; nCLB), and CBD levels were measured over the course of CBD treatment. CLB doses were recorded at baseline and at weeks 4 and 8 of CBD treatment. Side effects were monitored.

We report elevated CLB and nCLB levels in these subjects. The mean (± standard deviation [SD]) increase in CLB levels was 60 ± 80% (95% confidence interval (CI) [−2–91%] at 4 weeks); the mean increase in nCLB levels was 500 ± 300% (95% CI [+90–610%] at 4 weeks). Nine of 13 subjects had a >50% decrease in seizures, corresponding to a responder rate of 70%. The increased CLB and nCLB levels and decreases in seizure frequency occurred even though, over the course of CBD treatment, CLB doses were reduced for 10 (77%) of the 13 subjects. Side effects were reported in 10 (77%) of the 13 subjects, but were alleviated with CLB dose reduction.

A Phase I, open-label, randomized, crossover study in three parallel groups to evaluate the effect of Rifampicin, Ketoconazole, and Omeprazole on the pharmacokinetics of THC/CBD oromucosal spray in healthy volunteers

Stott et al 2013: https://doi.org/10.1186/2193-1801-2-236

- This Phase I study aimed to assess the potential drug-drug interactions (pharmacokinetic [PK] and safety profile) of Δ9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray (Sativex ®, nabiximols) in combination with cytochrome P450 (CYP450) inducer (rifampicin) or inhibitors (ketoconazole or omeprazole).
- Thirty-six healthy male subjects were divided into three groups of 12, and then randomized to one of two treatment sequences per group. Subjects received four sprays of THC/CBD (10.8/10 mg) alongside single doses of the CYP3A and 2C19 inducer rifampicin (600 mg), CYP3A inhibitor ketoconazole (400 mg) or CYP2C19 inhibitor omeprazole (40 mg). Plasma samples were analyzed for CBD, THC and its metabolite 11-hydroxy-THC (11-OH-THC).
- potential effects should be taken into consideration when co-administering THC/CBD spray with compounds which share the CYP3A4 pathway such as rifampicin or ketoconazole.

ProjectCBD.org
Free downloadable
“Primer on
Cannabinoid-Drug
interactions”

Adverse Events Using Cannabis

Reported Adverse Events

- Paranoia
- Anxiety/Panic Attack
- Dizziness
- Drowsiness
- Dry mouth
- Dry, red eyes
- Increased appetite
- Loss of Appetite
- Low blood pressure
- Increased heart rate

- Hypertension
- Sleepiness/Lethargy
- Insomnia
- Impaired memory
- Hallucinations
- Relapse of MS
- Vomiting
- UTI’s
- Diarrhea/Constipation
- Orthostatic Hypotension

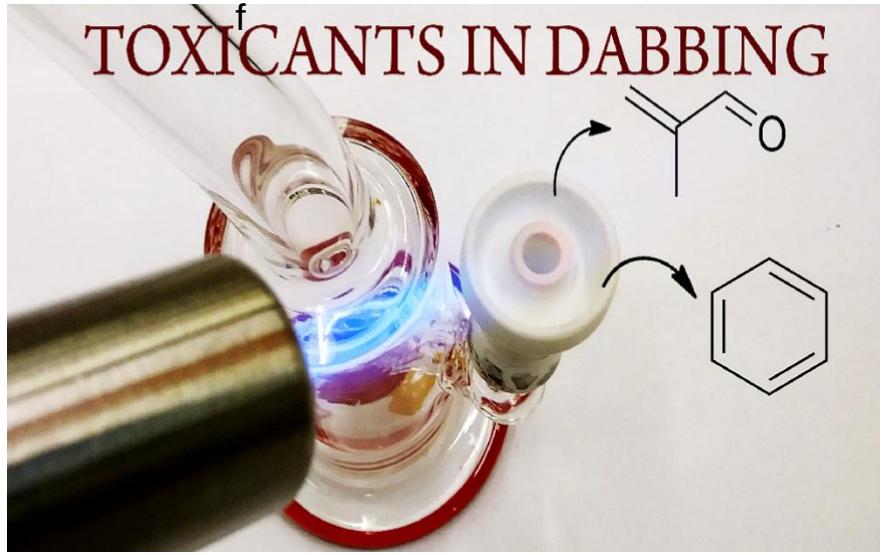
Factors Related to Adverse Events

- Dose used and content of cannabinoids and terpenes
  - Formulation
  - Route of administration
  - Experience and tolerance
  - Comorbid conditions
  - Drug-drug interactions
  - Genomics of the individual
  - Product contamination
  - Misbranded/labeled products
- Knowing **what to use** and **how to use** it is **key to avoiding** almost all **adverse events**

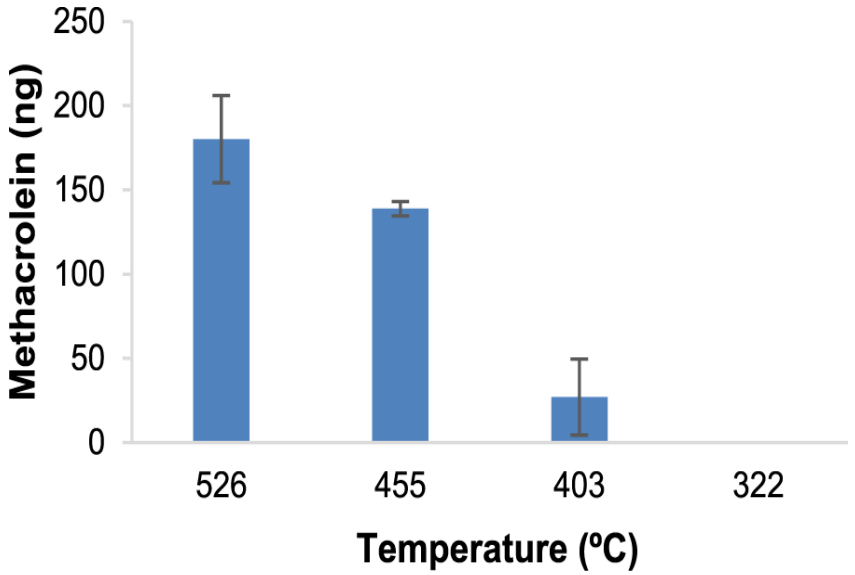
Vaporization Hazards

- Meehan-Atrash J, 2017: Toxicant Formation in Dabbing: The Terpene Story
  - Simulated ”dabbing” in an analytical setting to determine vaporization byproducts and compare to the atmospheric chemistry literature.
  - Used common cannabis terpenes (myrcene, Limonene, Linalool, and Blue River Extracts Fire OG mix) equivalent to a 40mg dab at 5.6% terps
  - Hot surface is generally not temperature controlled and higher temps create more toxins

http://pubs.acs.org/journal/acsodf

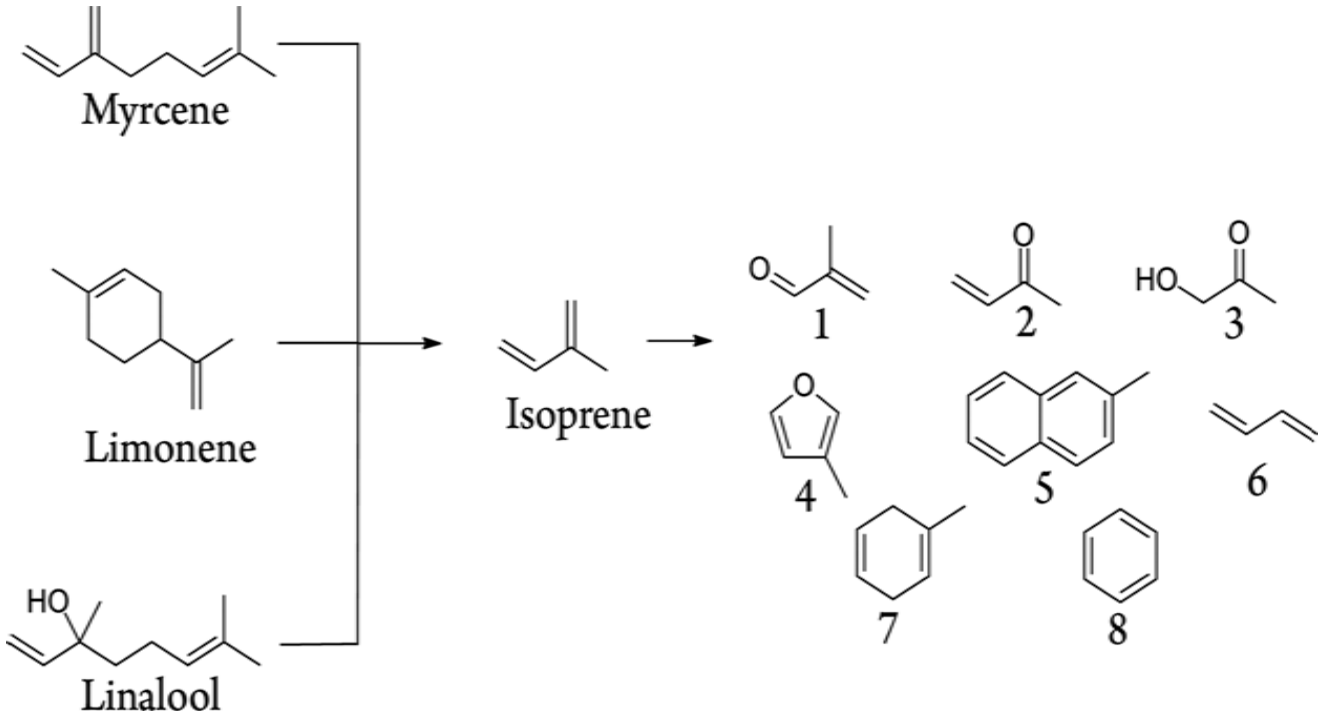


550°C	Methacrolein (ng/mg terpene)	Benzene (ng/mg terpene)
”Fire OG”	127	10
Limonene	261	63
Linalool	103	ND
Myrcene	81	60



Scheme 1. Terpene Degradation Products Identified via the GC−MS Analysis

https://pubs.acs.org/journal/acsodf



1, Methacrolein; 2, methyl vinyl ketone; 3, hydroxyacetone; 4, 3-methylfuran; 5, 2-methylnapthalene; 6, 1,3-butadiene; 7, 1-methylcyclohexa-1,4- diene; 8, benzene. These and other related products were produced from pure samples of each of limonene, linalool, and myrcene.

Vaporization Hazards

- Troutt W et al, 2017: Carbonyl Compounds Produced by Vaporizing Cannabis Oil Thinning Agents
  - Diluents used by E-cigarette makers and some cannabis vape cart producers
  - Evaluated propylene glycol [PG], vegetable glycerin [VG], polyethylene glycol 400 [PEG 400], **vitamin E acetate** and medium chain triglycerides [MCT], heated to 230°C and the resulting vapors were tested for acetaldehyde, acrolein, and formaldehyde
  - Carbonyl levels were measured in micrograms per puff
  - Results: use of PG and PEG 400 as a diluent produced high levels of acetaldehyde and formaldehyde (this is a no-no in responsible vape production)
  - Use of PEG 400 produced equivalent levels of formaldehyde from one inhalation as from smoking one cigarette.
- Takeaways today:
  - Do not use E-cigarettes, ever!
  - Do not use any cannabis extracts that are diluted with anything other than what comes out of the extraction process used.

Cannabis, Patient, Physician

Actions of Professional Licensing Boards

- NRS 453A.500 (Statutes)
  - Prohibited from taking disciplinary action against attending provider of healthcare in accordance with this chapter
    - Regardless of residence (Nevada or other State)
    - Must be diagnosed with a chronic or debilitating medical condition
  - You must:
    - Personal assessment of medical Hx and current medical condition
    - AND, as discussed possible risks and health benefits
    - There is no age restrictions for the use of medical of cannabis

https://www.leg.state.nv.us/NRS/NRS-453A.html#NRS453A

Qualifying Conditions

NRS 453A.050

- Cancer
- Aids
- Epilepsy and other illnesses that trigger seizures
- Glaucoma
- Multiple sclerosis or other persistent muscle spasms
- PTSD
- Severe/chronic pain
- Cachexia
- Severe nausea
- Additional conditions may be approved on request to the Department of Health and Human Services

https://www.leg.state.nv.us/NRS/NRS-453A.html#NRS453ASec050

4. Steps to Become a Medical Marijuana Patient

1. Diagnosed with Qualifying, Disabling or Chronic Condition
2. Valid State of Nevada Identification
3. Obtain a medical recommendation from an Attending provider of health care
4. Apply online ($50 for 1 year, $100 for two), http://dpbh.nv.gov

Most NV dispensaries will facilitate the application process for patients and process takes 30 days following submission for temp card

http://dpbh.nv.gov/Reg/MM-Patient-Cardholder-Registry/MM_Patient_Cardholder_Registry_-_Home/

http://dpbh.nv.gov/Reg/MM-Patient-Cardholder-Registry/dta/FAQs/Medical_Marijuana_Patient_Cardholder_Registry_-_FAQs/

Regulations for Possession

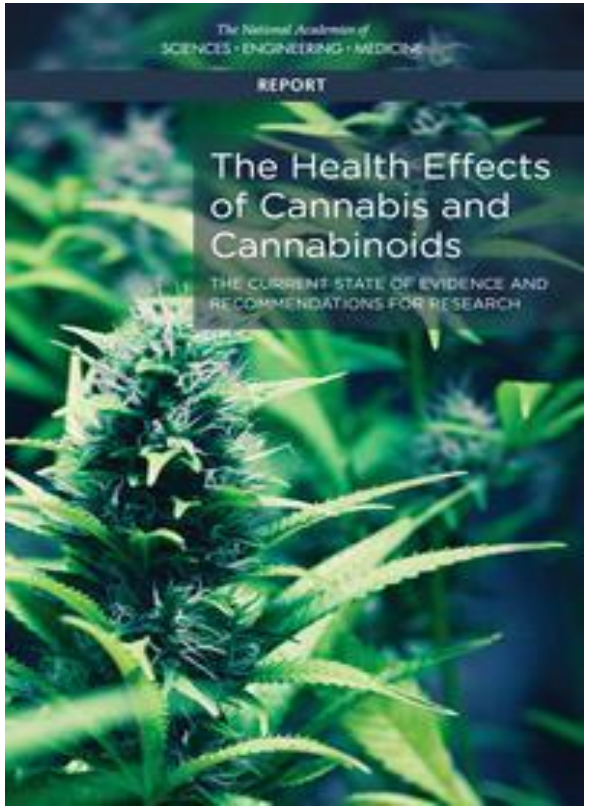
- **Medical patients** (Nevada Medical Marijuana Card)
  - Possess 2.5 oz usable cannabis in any one 14 day period
- **Adult use** (not participating in the medical program)
  - Possess 1 oz usable cannabis
  - and/or ⅛ oz of concentrate
- **Consuming cannabis**
  - not in a public place
  - Not in a moving vehicle (car, boat, etc.)

http://marijuana.nv.gov/Legal/PossessionAndConsumption/

The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research

- The committee reached nearly 100 research conclusions based on consideration of more than 10,000 research articles
- The committee found three medical applications for cannabis use supported by conclusive evidence:
  - Nausea and vomiting associated with cancer chemotherapy
  - Chronic pain in adults
  - Spasticity in multiple sclerosis

- http://www.nationalacademies.org/hmd/Reports/2017/health-effects-of-cannabis-and-cannabinoids.aspx



Qualifying Conditions of Medical Cannabis License Holders in the United States

Health Aff (Millwood). 2019 Feb; 38(2): 295–302. doi: 10.1377/hlthaff.2018.05266

Kevin F. Boehnke,a,* Saurav Gangopadhyay,b Daniel J. Clauw,a and Rebecca L. Haffajeec

Collected from state registry statistics comprising 20 states and Washington DC, up to April 2018 data on 813,917 registered patients.

85.5% of conditions for which patients are licensed to use medical cannabis have either substantial or conclusive evidence of efficacy.

Symptom & Condition

Cannabinoids associated with efficacy

Leafly

Reported Medical Applications for Cannabis

- ADHD
- Addiction/withdrawal
- AIDS/HIV
- Anorexia
- Anxiety
- Arthritis
- Autism Spectrum Disorder
- Autoimmune Disorders
- Bipolar Disorder
- Cachexia
- Cancer
- Chronic Pain
- Crohn's Disease
- Depression
- Epilepsy/Seizures
- Fibromyalgia
- Glaucoma
- Hypertension
- IBS/IBD
- Meniere's Disease
- Multiple Sclerosis
- Nausea/Emesis
- Neuropathic Pain
- OCD
- Parkinson's Disease
- PMS/PCOS
- PTSD
- Psychosis/Schizophrenia
- Sleep Disorders
- Wellness/proactive medicine

Oral Cannabidiol Use in Children With Autism Spectrum Disorder to Treat Related Symptoms and Co-morbidities

*Dana Barchel1†, Orit Stolar2†, Tal De-Haan1, Tomer Ziv-Baran3, Naama Saban4, Danny Or Fuchs1, Gideon Koren1,5 and Matitiahu Berkovitch1**
Front. Pharmacol., 09 January 2019 | https://doi.org/10.3389/fphar.2018.01521

- Report on the experience of parents who administer, under supervision, oral cannabinoids to their children with ASD
- 53 children at a median age of 11 (4–22) year received cannabidiol for a median duration of 66 days (30–588). 45 males, 8 females
- **Self-injury and rage** attacks (*n* = 34) improved in 67.6% and worsened in 8.8%.
- **Hyperactivity** symptoms (*n* = 38) improved in 68.4%, did not change in 28.9% and worsened in 2.6%.
- **Sleep** problems (*n* = 21) improved in 71.4% and worsened in 4.7%. Anxiety (*n* = 17) improved in 47.1% and worsened in 23.5%.
- An **overall improvement** was reported in 74.5%. No change was reported in 21.6% and worsening in 3.9%.
- **Adverse effects**, mostly somnolence (n=12) and change in appetite (n=10) were mild.

Routes of Administration

Different Ways to Use Medical Marijuana

- Combustion smoking
- Vaporization
- Edible forms
- Capsules
- Sublingual, tinctures, buccal absorption
- Transdermal patches
- Topical Creams
- Suppositories

Vaporization & Combustion Smoking

*Quick onset (1-5 minutes), short duration of effects (1-2 hours), this method may produce psychoactive effects.

*Vaporizers are the logical choice for moderate to experienced and/or health-conscious cannabis consumers.

*A vaporizer steadily heats herbs to a temperature that is high enough to extract THC, CBD, and other cannabinoids, but the temperatures are too low to create the potentially harmful toxins that are released during combustion.

*Essentially, vaporization minimizes the health risks associated with smoking.

Strategies to standardize the pulmonary route

PPP001

General Observations with Inhalation/Vaporization

- n=6
- THC and CBD detectable in plasma 1 minute after inhalation
- Remained detectable up to 3 hrs post-administration
- Cmax: 30 to 180 ng/ml
- Tmax: 5 min post-administration
- Steady state was not achieved after multiple doses

Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly.

Abuhasira R[1], Schleider LB[2], Mechoulam R[3], Novack V

INTRODUCTION:

There is a substantial growth in the use of medical cannabis in recent years and with the aging of the population, medical cannabis is increasingly used by the elderly. We aimed to assess the characteristics of elderly people using medical cannabis and to evaluate the safety and efficacy of the treatment.

RESULTS:

During the study period, 2736 patients above 65 years of age began cannabis treatment and answered the initial questionnaire. The mean age was 74.5 ± 7.5 years. The most common indications for cannabis treatment were pain (66.6%) and cancer (60.8%). After six months of treatment, 93.7% of the respondents reported improvement in their condition and the reported pain level was reduced from a median of 8 on a scale of 0-10 to a median of 4. Most common adverse events were: dizziness (9.7%) and dry mouth (7.1%). After six months, 18.1% stopped using opioid analgesics or reduced their dose.

CONCLUSION:

Our study finds that the therapeutic use of cannabis is safe and efficacious in the elderly population. Cannabis use may decrease the use of other prescription medicines, including opioids. Gathering more evidence-based data, including data from double-blind randomized-controlled trials, in this special population is imperative.

EurJ Intern Med. 2018 Mar;49:44-50. doi: 10.1016/j.ejim.2018.01.019.

Edible Forms of Marijuana & Capsules

*Long onset (1-2 hours), longer duration of effects (6-8 hours), may produce psychoactive effects and cause the most drowsiness.

*Eating or drinking cannabis provides significantly different effects from delivery methods that immediately enter the bloodstream, such as smoking or vaping.

*Edibles can be defined as any food that contains cannabis, these products have longer onsets and tend to cause powerful full-body, psychoactive effects.

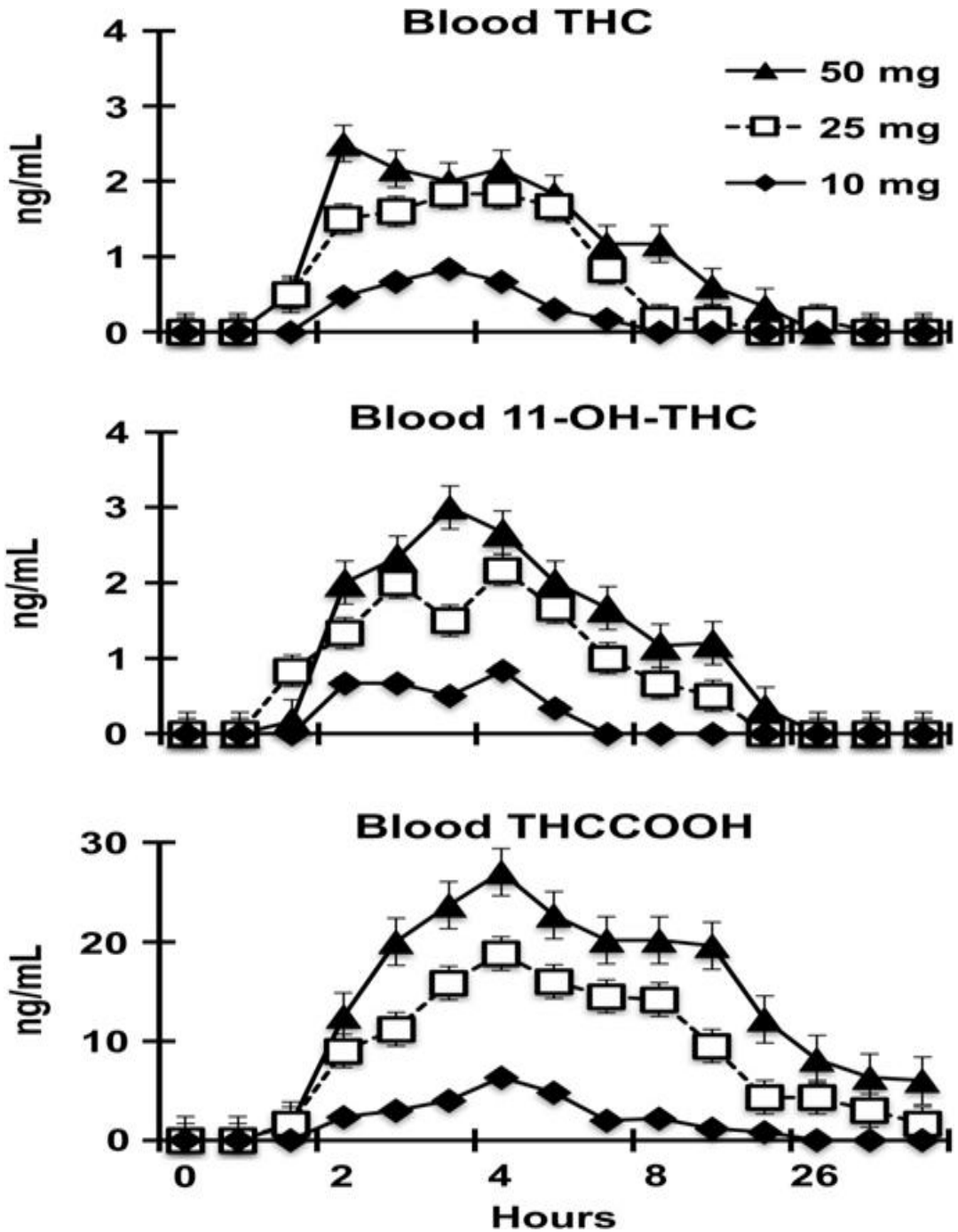
*Most often, edibles are infused with a staple infused ingredient high in fat — like **butter** or **olive oil** — that enable extraction of the plant's therapeutic properties.

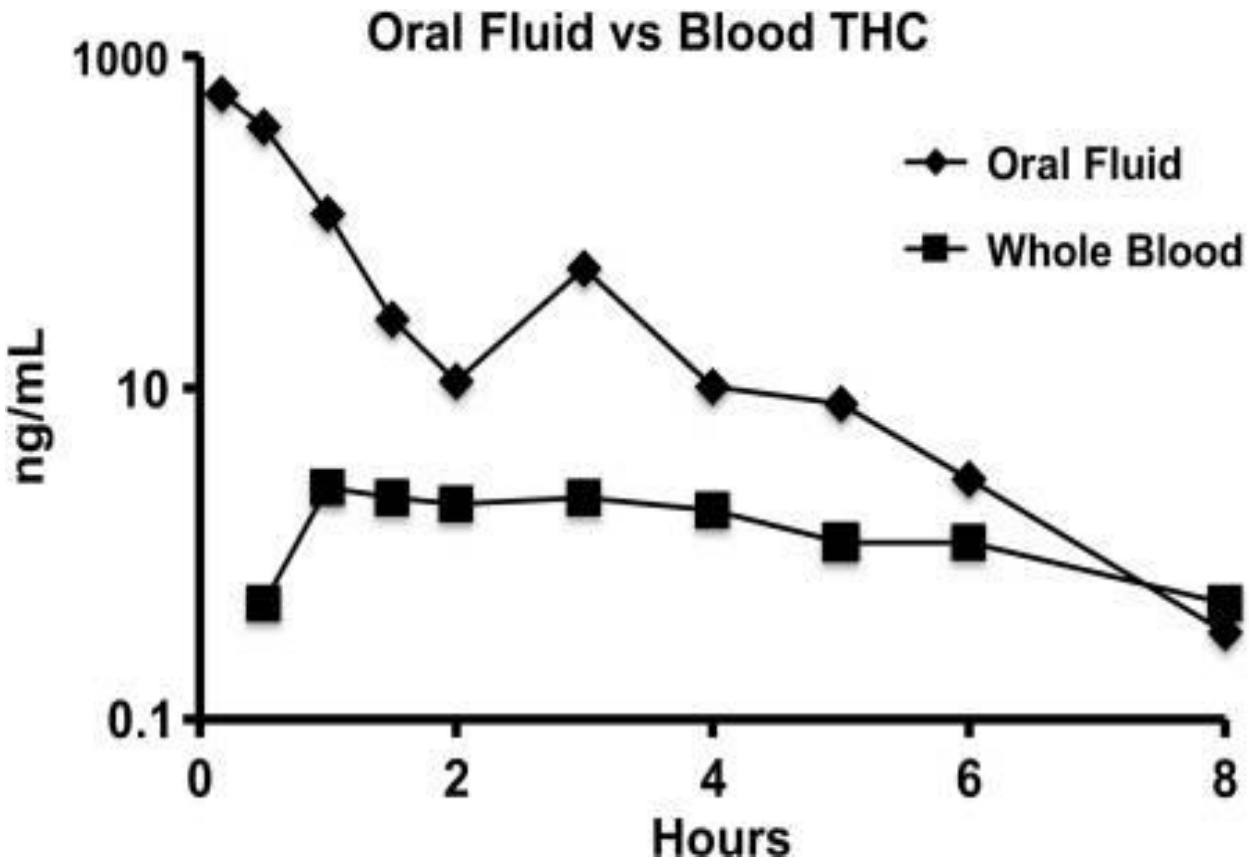
Pharmacokinetic Profile of Oral Cannabis in Humans: Blood and Oral Fluid Disposition and Relation to Pharmacodynamic Outcomes

J Anal Toxicol. 2017 Mar; 41(2): 83–99. Published online 2017 Feb 3. doi: 10.1093/jat/bkx012

Ryan Vandrey,1 Evan S. Herrmann,2 John M. Mitchell,3 George E. Bigelow,1 Ronald Flegel,4 Charles LoDico,4 and Edward J. Cone1

- Double-blind, between-subjects design was used to evaluate three doses: 10, 25 and 50 mg of THC (NIDA 11% cannabis ground up into brownie mix
- Low fat breakfast with brownie
- n=18, sex balanced, mean age 26 yr old
- THC in whole blood mean Cmax: 1, 3.5 and 3.3 ng/ml
- THC in whole blood mean Tmax: 0.9, 2.6 and 2.3 hrs (0-6hrs)
- Detectable in blood up to 22 hrs after single dose





J Anal Toxicol. 2017 Mar; 41(2): 83–99

Tinctures, Sublinguals & Buccal Absorption

- Tinctures are essentially a topical application that is administered through the mouth, and they are immediately absorbed into the bloodstream unlike edibles or drinks.
- In tinctures alcohol is used as the solvent (any proof greater than 80 can be used effectively).
- In sublingual drops other fat-soluble liquids are used, such as coconut, hemp, MCT, olive oil or glycerine.
- Generally, a few drops to 2 ml of the solution are placed under the tongue, where it's absorbed into the body versus swallowed and digested.
- Longer onset (30 min to 1 hour), and longer duration of effects (1-4 hours), this method also may produce psychoactive effects.
- Buccal Absorption; faster onset, duration 4-6 hours, higher bioavailability, consistent delivery route

- **Standardized Sublingual and buccal products**

Klumpers et al., 2011

Crowley, DeVries and Moreno-Sanz, 2018


strainz
RATIO TINCTURES
1:5
CBD | THC
20mg CBD
100mg THC
1:1
100mg CBD
100mg THC
20:1
500mg CBD
25mg THC
THC


CANNABIS INFUSED TINCTURE
DRIFT AWAY
300 MG THC
CA
Fractionated
COCONUT OIL
1 fl oz / 29.6ml


Trokie
Pain Relief
CBD SPRAY
First Aid Wound Care
300 MG CBD
Trokie
Pain Relief
CBD SPRAY
Tattoo Care
300 MG CBD
Trokie
Pain Relief
CBD SPRAY
Cooling Action
300 MG CBD


BAYER
SATIVEX
Oromucosal Spray
Bayer HealthCare
3 x 10 ml Spray Containers
QW

Transdermal Patches & Creams

*These methods generally do not produce psychoactive effects.

* Topical administration usually utilizes whole plant cannabis extracts — many times in combination with other herbs and essential oils for synergistic benefits

*Topical effects differ from other medicating methods in that they don’t provide the cerebral stimulation that users describe as “being high.” Because of this, topicals are appropriate for consumers needing a clear head and localized relief (for example, muscle aches or soreness).

Tips for New Patients

1. Micro-dose - start with 1-5mg
2. Patience - wait 3 hours before taking more.
3. Awareness of last meal; full stomach vs empty
4. CBD is an antidote to THC intoxicating effects.
5. Buddy system for first time.

What is a good starting dose?

*Most patients naive to cannabis should begin with CBD for 1 to 3 days and then add THC, generally at a 2.5mg dose, starting near bedtime, if CBD is not achieving desired results.

***Start low and go slow!**

*Different delivery methods have different onset and duration times so be cautious **(edibles delayed vs buccal faster acting)**

*Pay attention to THC:CBD ratios when trying new products.

Laboratory Testing

Laboratory Testing - A Requirement

- Potency (top 10)
- Pesticide Analysis
- Residual Solvents
- Heavy Metals
- Moisture Content
- Microbial Analysis
- Terpene Profiling
- Mycotoxin Analysis

Lab Equipment

- LC-MS/MS
- GC-MS/MS
- GC-FID
- GC-MS
- LC-MS
- ICP-MS (Inductively coupled plasma mass spectrometry)
- Graphite furnace atomic absorption spectroscopy
- PCR (Polymerase chain reaction)
- Moisture Balance

Certificate of Analysis

Powered by Confident Cannabis
1 of 2

Silver State Trading

Sparks, NV 89431
cheyenne@silverstatetrading.com
(775) 335-2033
Lic. #65990416749820182121

Sample: 1809TSF0059.4220

Strain: LA Affie
Batch #: LA081518; Lot #: LOT1448;
Sample Received: 09/14/2018; Report Generated: 09/18/2018
Harvest/Production Date: 08/15/2018

LA Affie

Plant, Flower - Cured, Indoor
Harvest Process Lot: ; METRC Batch: 1A4040300000D49000001059; METRC Sample: 1A4040300000D49000001060

The photo on this report is of a sample collected by the lab and may vary from the final packaging.

Safety

Pass — Pesticides	Pass — Microbials	Pass — Mycotoxins
Not Tested — Solvents	Pass — Heavy Metals	Pass — Foreign Matter

Cannabinoids

21.72%	0.06%	9.4 %
Total Potential THC	Total Potential CBD	Moisture

Cannabinoid	LOQ	Mass	Mass
	%	%	mg/g
THCa	0.05	23.79	237.9
Δ9-THC	0.05	0.86	8.6
CBD	0.05	<LOQ	<LOQ
CBDa	0.05	0.07	0.7
CBC	0.05	<0.05	<0.5
CBG	0.05	<LOQ	<LOQ
CBN	0.05	<LOQ	<LOQ
THCV	0.05	<LOQ	<LOQ
CBGa	0.05	<0.05	<0.5
Total		24.71	247.1

Terpenes

Orange | Cinnamon | Lavender

Terpene	LOQ	Mass	Mass
	%	%	mg/g
δ-Limonene	0.05	0.90	9.0
β-Caryophyllene	0.05	0.68	6.8
Linalool	0.05	0.31	3.1
β-Myrcene	0.05	0.20	2.0
β-Pinene	0.05	0.14	1.4
α-Humulene	0.05	0.10	1.0
α-Pinene	0.05	0.08	0.8
α-Bisabolol	0.05	<0.05	<0.5
Caryophyllene Oxide	0.05	<0.05	<0.5
Ocimene	0.05	ND	ND
Terpinolene	0.05	<0.05	<0.5
trans-Nerolidol	0.05	<0.05	<0.5
Total		2.41	24.1

10 Greg St
Sparks, NV
(844) 374-5227
http://www.374labs.com

Dr. Jeff Angermann
Scientific Director

All pass limits are as specified in NAC 453.A and DPBH Policies. Unless otherwise stated all quality control samples performed within specifications established by the Laboratory. This product has been tested by 374 Labs, LLC (MME# 03754325902079441647) using valid testing methodologies and a quality system as required by Nevada state law. Values reported relate only to the product tested. 374 Labs makes no claims as to the efficacy, safety or other risks associated with any detected or non detected levels of any compounds reported herein. This Certificate shall not be reproduced except in full, without the written approval of 374 Labs. Uncertainty information is available upon request. 374 Labs complies with ISO/IEC 17025 standards. Potency performed per SOP-000001, Terpenes performed per SOP-000002, Metals performed per SOP-000003, Microbial testing performed per SOP-000004, Pesticides performed per SOP-000005. Moisture per SOP-000006. Photo is of sample collected by the lab and may vary from final packaging.

Certificate of Analysis

Powered by Confident Cannabis
2 of 2

Silver State Trading

Sparks, NV 89431
cheyenne@silverstatetrading.com
(775) 335-2033
Lic. #65990416749820182121

Sample: 1810TSF0146.5346

Strain: Citrus Sap
Batch #: CS102518; Lot #: LOT1494;
Sample Received: 10/25/2018; Report Generated: 10/30/2018
Harvest/Production Date: 10/25/2018

Citrus Sap

Plant, Trim, Indoor
Harvest Process Lot: LOT1494; METRC Batch: 1A4040300000D49000001253; METRC Sample: 1A4040300000D49000001254

Pesticides — Pass

Analyte	Mass	LOQ	Limit	Status
	PPM	PPM	PPM	
Abamectin	ND	0.003	0.050	Pass
Acequinocyl	ND	0.020	4.000	Pass
Beta-Cyfluthrin	ND	0.020	4.000	Pass
Bifenazate	ND	0.750	15.000	Pass
Bifenthrin	ND	0.003	0.050	Pass
Captan	NR	0.003	0.050	NT
Cyfluthrin	ND	0.020	4.000	Pass
Cypermethrin	ND	0.003	0.050	Pass
Daminozide	ND	0.050	0.050	Pass
Dimethomorph	ND	3.000	60.000	Pass
Etoxazole	ND	0.350	7.000	Pass
Fenhexamid	ND	1.500	30.000	Pass
Flonicamid	ND	0.350	7.000	Pass
Fludioxonil	ND	0.001	0.020	Pass
Imidacloprid	ND	0.003	0.050	Pass
Myclobutanil	ND	0.450	4.000	Pass
Paclobutrazol	ND	0.010	0.050	Pass
Piperonyl Butoxide	ND	0.100	2.000	Pass
Plant Growth Regulators	ND			Tested
Pyrethrins	ND	0.050	1.000	Pass
Quintozene	ND	0.010	0.200	Pass
Spiretoram	ND	0.085	1.700	Pass
Spirosad	ND	0.085	1.700	Pass
Spirotetramat	ND	0.050	10.000	Pass
Thiamethoxam	ND	0.001	0.020	Pass
Trifloxystrobin	ND	0.550	11.000	Pass

Heavy Metals — Pass

Analyte	Mass	LOQ	Limit	Status
	PPM	PPM	PPM	
Arsenic	ND	0.460	2.000	Pass
Cadmium	ND	0.230	0.820	Pass
Lead	ND	0.310	1.200	Pass
Mercury	ND	0.120	0.400	Pass

Microbials — Pass

Analyte	Units	Limit	Status
	CFU/g	CFU/g	
Aspergillus flavus	ND	1	Pass
Aspergillus fumigatus	ND	1	Pass
Aspergillus niger	ND	1	Pass
Aspergillus terreus	ND	1	Pass
Total Enterobacteriaceae	ND	1000	Pass
Total Coliforms	10	1000	Pass
Pathogenic E. Coli	ND	1	Pass
Salmonella	ND	1	Pass
Total Yeast & Mold	ND	10000	Pass

Residual Solvents — Not Tested

Analyte	Mass	LOQ	Limit	Status

Mycotoxins — Pass

Analyte	Mass	LOQ	Limit	Status
	PPM	PPM	PPM	
Aflatoxins	ND	0.00	0.02	Pass
B1	ND	0.00		Tested
B2	ND	0.00		Tested
G1	ND	0.00		Tested
G2	ND	0.00		Tested
Ochratoxin A	ND	0.00	0.02	Pass
Total Mycotoxins	ND		0.02	Pass

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All pass limits are as specified in NAC 453.A and DPBH Policies. Unless otherwise stated all quality control samples performed within specifications established by the Laboratory. This product has been tested by 374 Labs, LLC (MME# 03754325902079441647) using valid testing methodologies and a quality system as required by Nevada state law. Values reported relate only to the product tested. 374 Labs makes no claims as to the efficacy, safety or other risks associated with any detected or non detected levels of any compounds reported herein. This Certificate shall not be reproduced except in full, without the written approval of 374 Labs. Uncertainty information is available upon request. 374 Labs complies with ISO/IEC 17025 standards. Potency performed per SOP-000001, Terpenes performed per SOP-000002, Metals performed per SOP-000003, Microbial testing performed per SOP-000004, Pesticides performed per SOP-000005. Moisture per SOP-000006. Photo is of sample collected by the lab and may vary from final packaging.

Case Studies

Case Study: Minor Cannabinoid Impact

- Patient: Male, mid-30's, 8 seizures per day
- CBD/THC 3:1 solution, 40mg/mL, no terpenes, MCT oil, Diamond OG:
  - seizure-free for 9 weeks
- Next batch of 3:1 oil, Lemonade Haze:
  - seizures re-start immediately
- THC came from two different cultivars: Diamond OG and Lemonade Haze

	CBD	THC	THCA	CBDA	CBN	CBG	THCV	**CBGA**	**CBC**
Diamond OG	300	100	15.3	0.00	0.66	1.76	0.73	**0.99**	**0.00**
Lemonade Haze	300	100	15.6	0.00	0.45	1.62	1.19	**0.00**	**1.06**

Something to Think About

- Cannabis: An adaptogenic herb and disease state modifying
- Cannabis has a huge therapeutic index with no LD50
- Cannabis is a Federally Scheduled I drug (i.e. Heroin, Ecstasy, LSD, etc.)
- POLITICS and SPECIAL INTEREST, not Evidence Based Medicine results in it's Prohibition and scheduled I drug status
- The Endocannabinoid System: Homeostasis - Life, Balance
- Cannabis has been used for thousands of years in multiple cultures
- Cannabis was in top 3 prescriptions by physicians in the USA before 1932
- Cannabis was in the US Pharmacopeia: 1850 to 1942
- Educate, Embrace, Empower

THANK YOU!

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