



Cannabis as a plant: Taxonomy and Chemistry

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Disclaimer & Disclosure

- I am a member of the faculty at the University of Vermont
- Materials presented here represent my own findings, views and opinions and should not be taken as a statement, position, opinion, or endorsement by the University of Vermont

University of Vermont Health Network

Discussion includes investigational drugs not approved for use in the United States.

DISCLOSURE:

Is there anything to disclose? **Yes**

Please list the Potential Conflict of Interest (*if applicable*): **Relationships with Vermont Patients Alliance and Phytoscience Institute**

All Potential Conflicts of Interest have been resolved prior to the start of this program. **Yes**

(If no, credit will not be awarded for this activity.)

All recommendations involving clinical medicine made during this talk were based on evidence that is accepted within the profession of medicine as adequate justification for their indications and contraindications in the care of patients. **Yes**

Cannabis history

Human use

12,000-10,000 years ago *Cannabis* cultivation begins

1753 Linnaeus classifies *Cannabis sativa* L.

2011 First *Cannabis* genome is sequenced

Policy

1930 Harry Anslinger began the process of criminalization and prohibition of drugs including marijuana and by 1931 29 states had outlawed *Cannabis*.

1970 Controlled Substances Act passed. Cannabis is Schedule one drug categorized to have a high potential for abuse and no medicinal value.

1996 Passage of the Compassionate Use Act initiative

Medical discovery

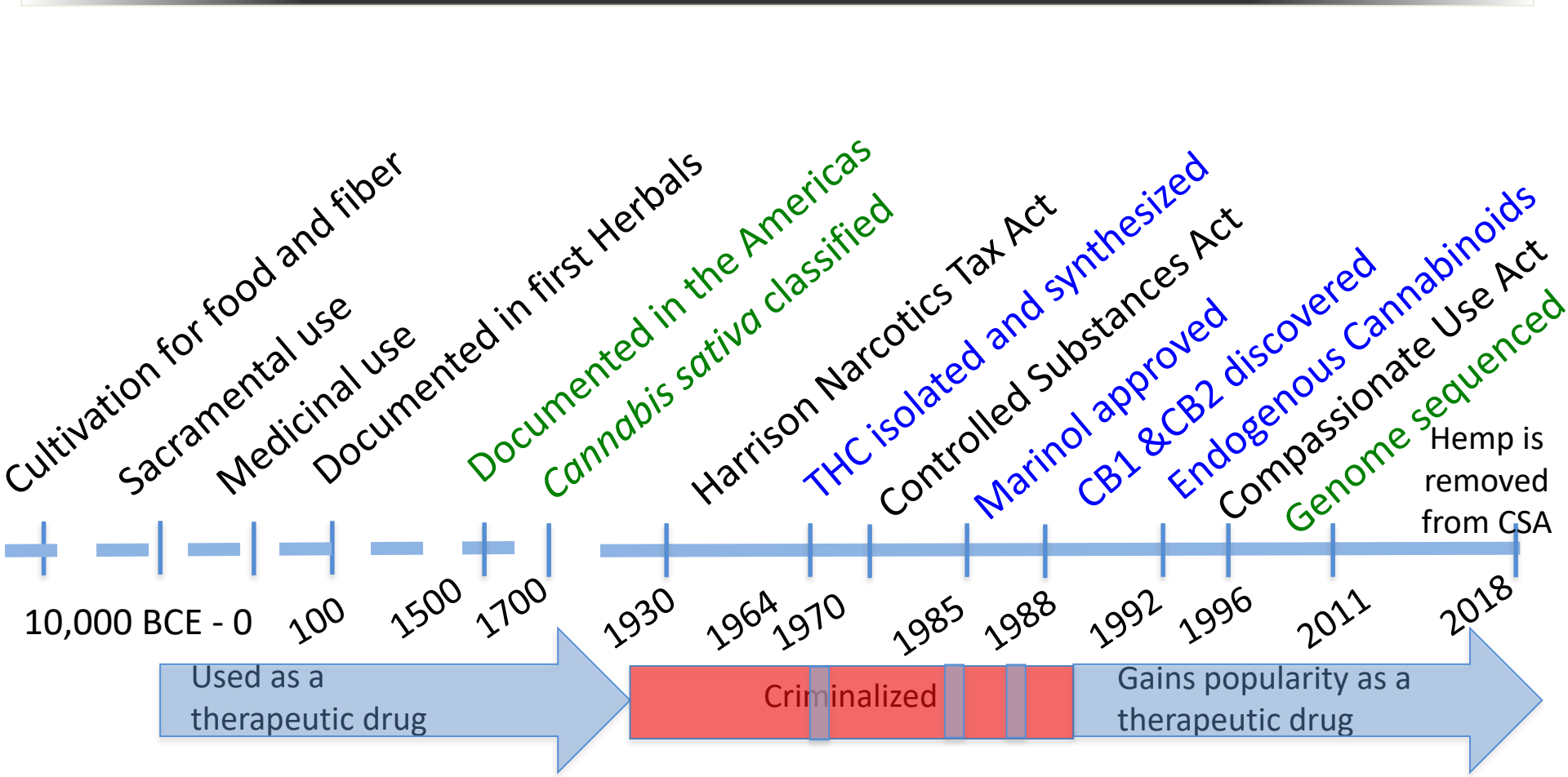
1964 Tetrahydrocannabinol (THC) is isolated and synthesized

1988 Cannabinoid receptors CB1 and CB2 discovered

1992 Endogenous cannabinoids discovered

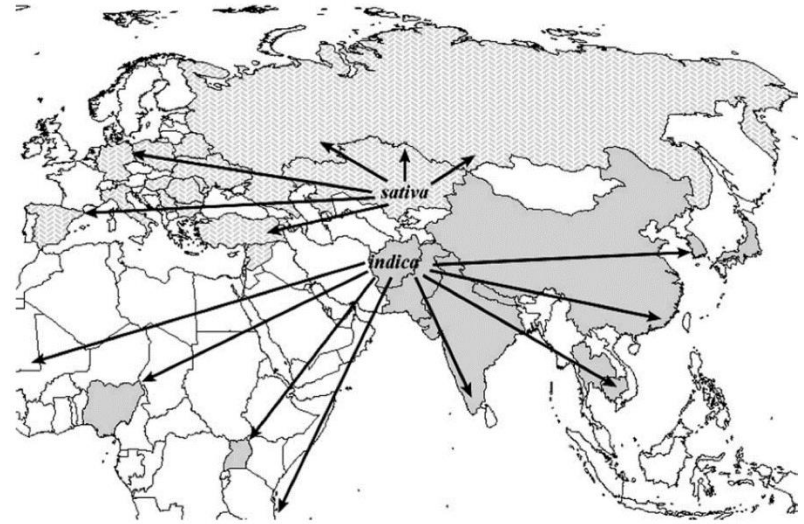


Cannabis history



Cannabis history

- The ancestral distribution of *Cannabis* is central Asia (Li, 1974)
- *Cannabis* arrived in the Americas after 1545 (Small et al., 1975)
- Currently *Cannabis* is distributed world-wide



Cannabis plant biology

Macroscopic morphological characters

- Leaves, flowers, and fruit



Photo credit: <http://en.wikipedia.org/wiki/Cannabis>

Cannabis plant biology

Microscopic morphological characters

- Trichomes and glands

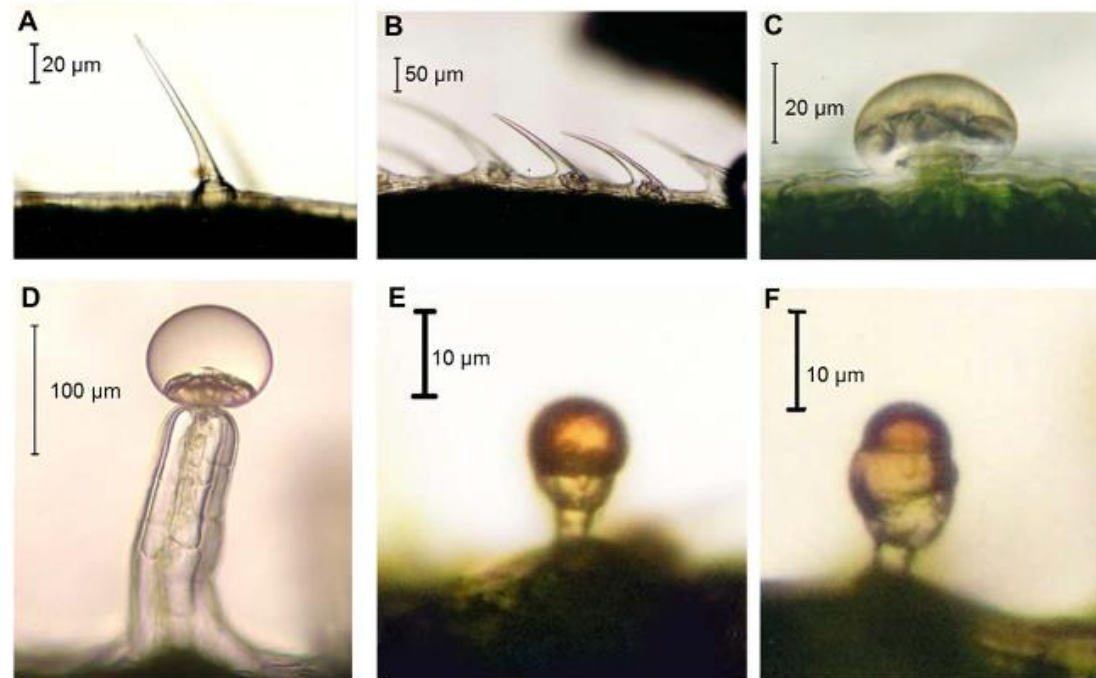


FIGURE 3 | Hemp trichome types. (A) Unicellular non-glandular trichome; (B) cystolythic trichomes; (C) capitate sessile trichome; (D) capitate-stalked trichome; (E) simple bulbous trichome; (F) complex bulbous trichome. Images kindly provided by Dr. David J. Potter.

Cannabis plant biology

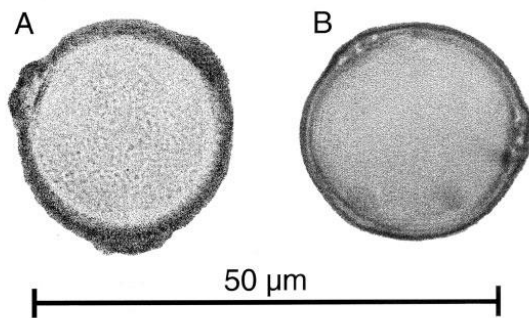
Reproductive characters

- Male and female flowers are found on different plants
- Wind Pollinated



Female flower

Male flower



Pollen

Cannabis plant biology

Plants produce chemical compounds, phytochemicals, as part of their normal metabolic activities.

Phytochemicals are divided into two groups:

1. Primary metabolites

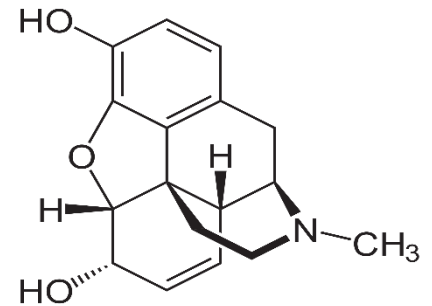
- found in all plants, serve basic plant functions
- i.e. sugars and fats

2. Secondary metabolites

- found in select plants, serve in a more specific function
- i.e. opium, phytocannabinoids



Wounded poppy fruit exuding opium



Morphine, the active principle of opium

Cannabis plant biology

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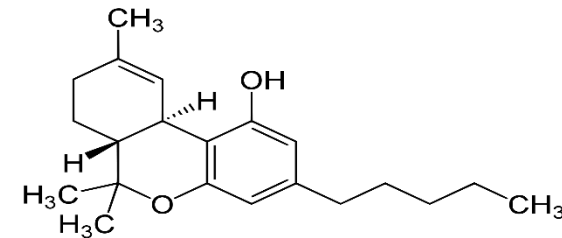
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- i.e. opium, phytocannabinoids

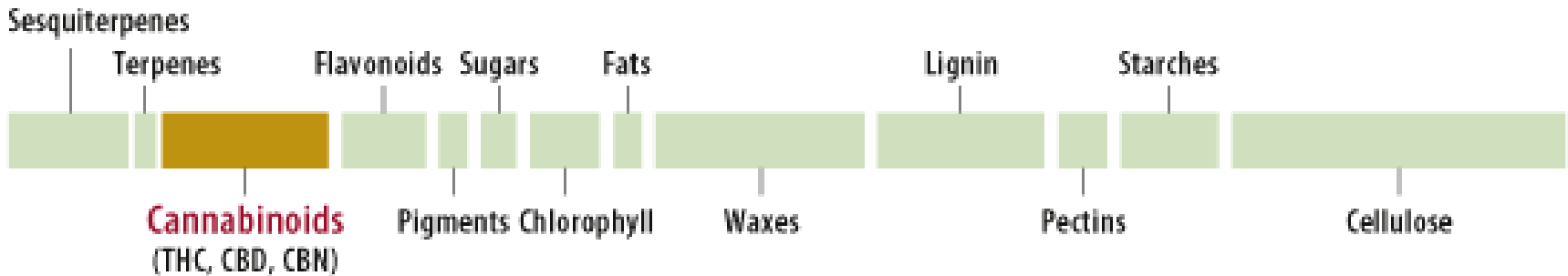


Cannabis glandular trichomes containing phytocannabinoids



Delta-9-tetrahydrocannabinol, one active principle of *Cannabis*

Cannabis chemicals

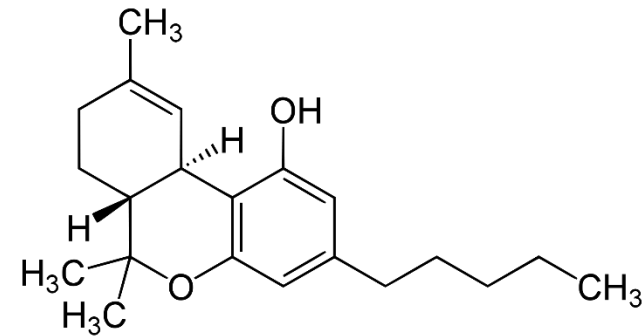


Cannabis chemicals

The main biologically active phytocannabinoids

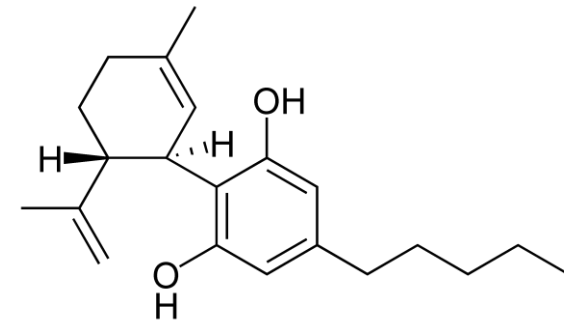
Delta-9-tetrahydrocannabinol (THC)

- Partial Agonist CB1/CB2 receptors
- Psychoactive
- Anti-pain, anti-nausea
- Anti-spasm, anti-immune



Cannabidiol (CBD)

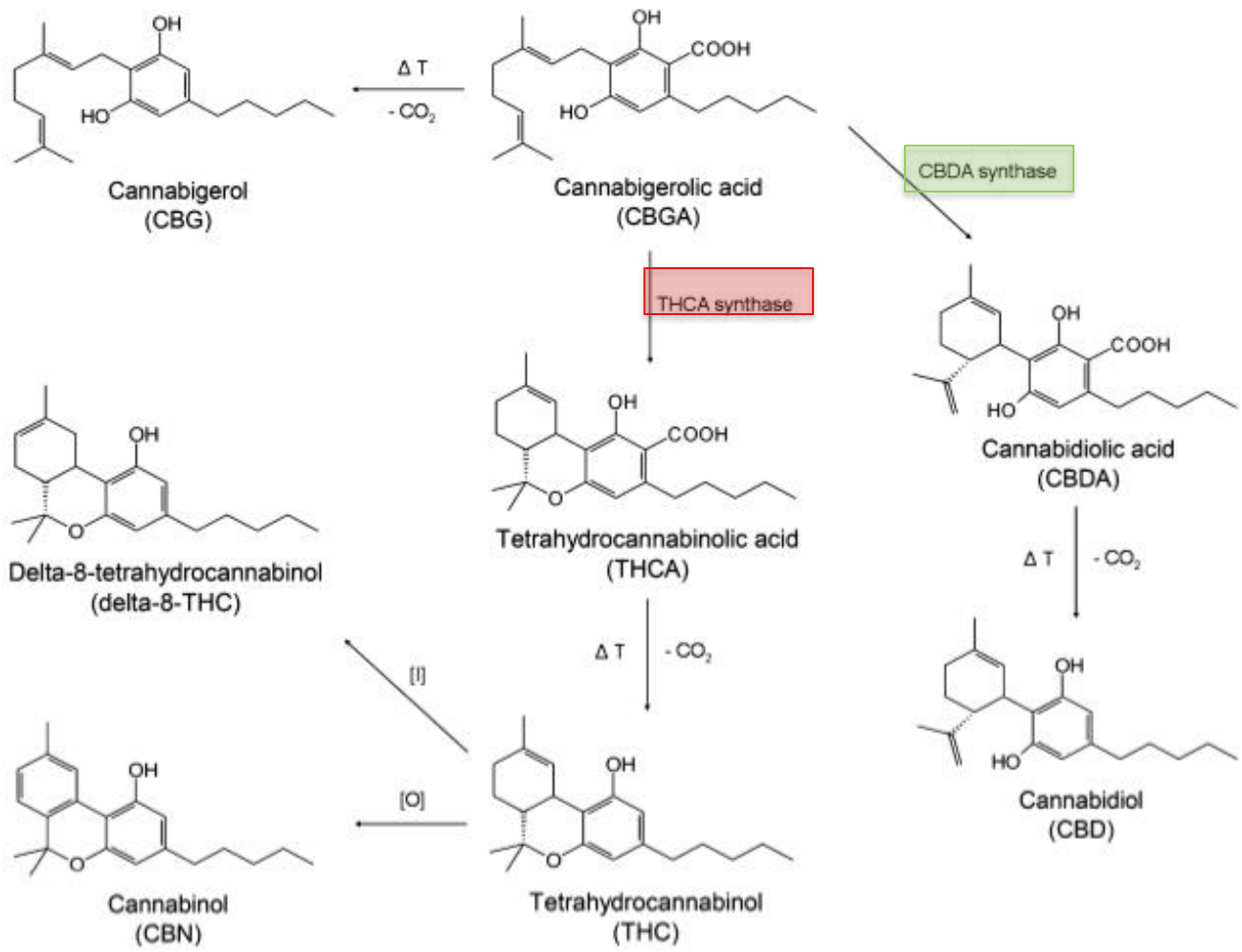
- Antagonist CB1/CB2 receptors
- Not psychoactive
- Anti-seizure activity



Activated by heating the plant

Cannabis chemicals

What are Phytocannabinoids?

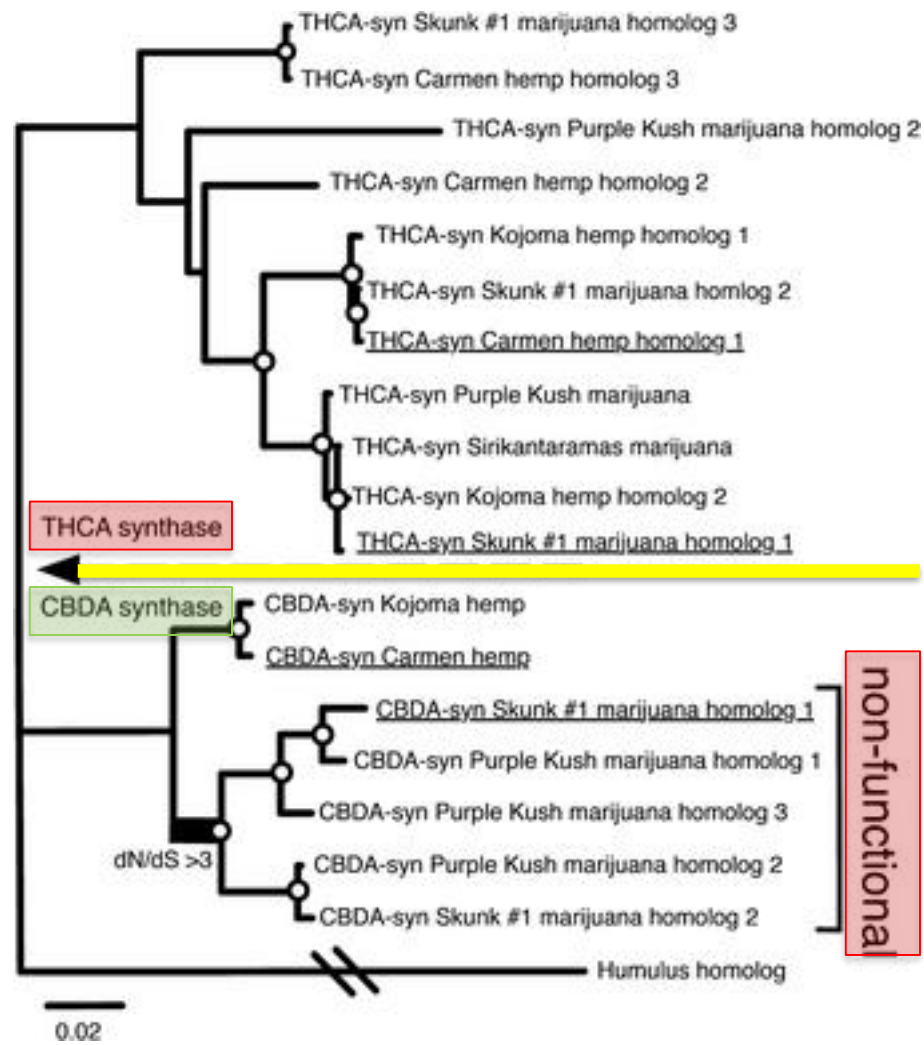


Cannabis chemicals

How are Phytocannabinoids manufactured by the plant?

Phytocannabinoid biosynthesis

1. Chemical precursors are absorbed through the roots from the soil
2. CBD & THC derive from CBG compounds, catalyzed by the enzyme THCA synthase or CBDA synthase
 - CBDA synthase is dominant
 - Hemp has THCA & CBA synthase
 - Drug-type (Marijuana) has THCA & CBDA synthase
 - **nonfunctional** CBDA synthase

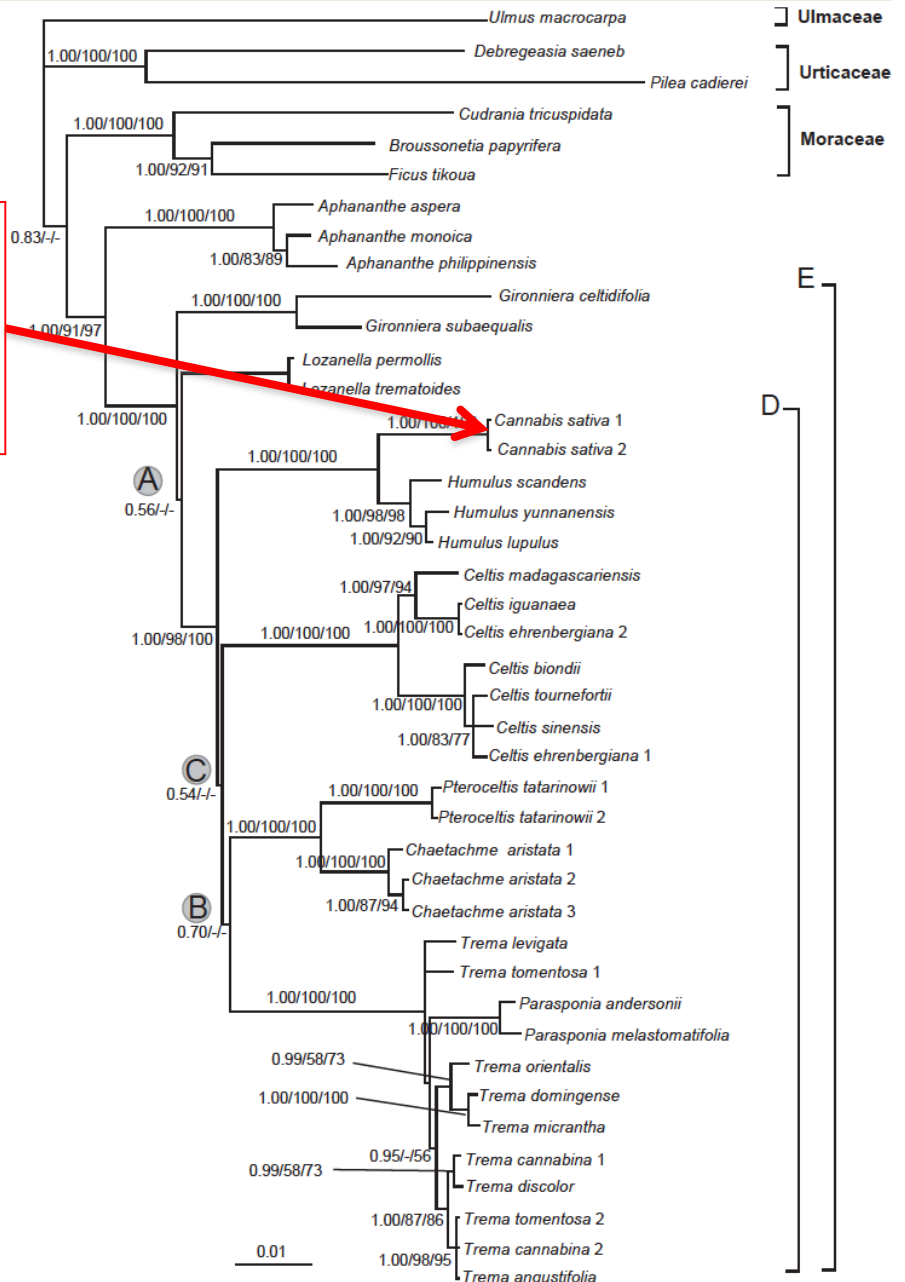


Source: Weilben et al., 2015


Cannabis chemicals

Phytocannabinoids evolved in *Cannabis*

Herbivory defense?
Environmental response?

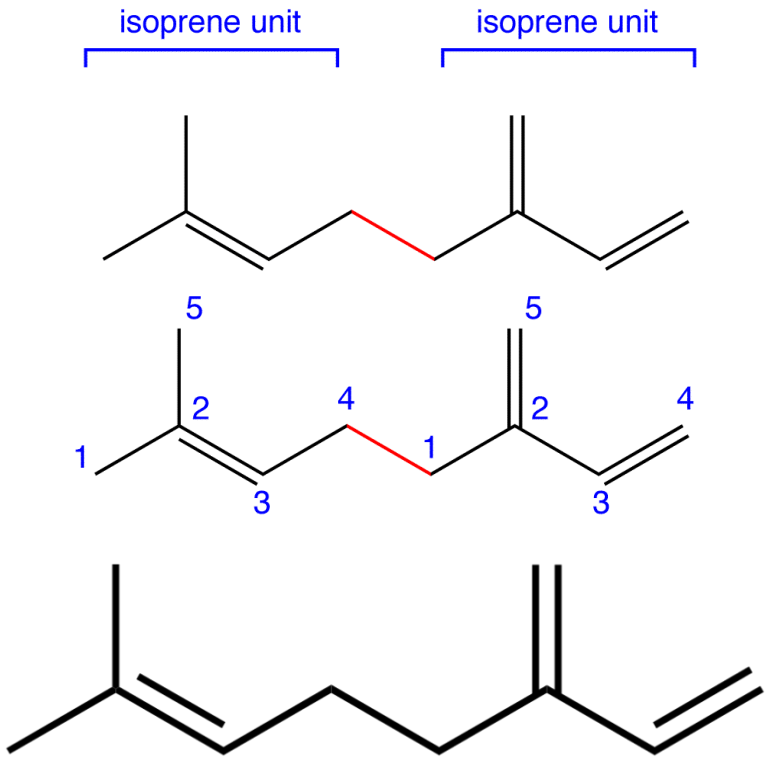


Cannabis chemicals

No.	Groups	Number of Known Compounds
1	CBG type	17
2	CBC type	8
3	CBD type	8
4	Δ^9 -THC type	18
5	Δ^8 -THC type	2
6	CBL type	3
7	CBE type	5
8	CBN type	10
9	CBND type	2
10	CBT type	9
11	Miscellaneous	22
12	Total cannabinoids	104
13	Total noncannabinoids	441 
	Total	545

Cannabis chemicals

What are the non-cannabinoids?



Terpenes
(Myrcene)

Cannabis chemicals

Myrcene has an analgesic effect




Journal of Ethnopharmacology

Volume 34, Issue 1, August 1991, Pages 43–48



Myrcene mimics the peripheral analgesic activity of lemongrass tea

Berenice B. Lorenzetti^a, Glória E.P. Souza^b, Sílvia J. Sarti^c, David Santos Filho^c, Sérgio H. Ferreira  ^a


“Terpenes such as myrcene may constitute a lead for the development of new peripheral analgesics with a profile of action different from that of the aspirin-like drugs.”

Cannabis chemicals

α -Pinene appears to be a broad-spectrum antibiotic



Characterization and antimicrobial activity of essential oils of industrial hemp varieties (*Cannabis sativa* L.)

Lorenzo Nissen^a,  , Alessandro Zatta^b, Ilaria Stefanini^a, Silvia Grandi^b, Barbara Sgorbati^a, Bruno Biavati^a, Andrea Monti^b

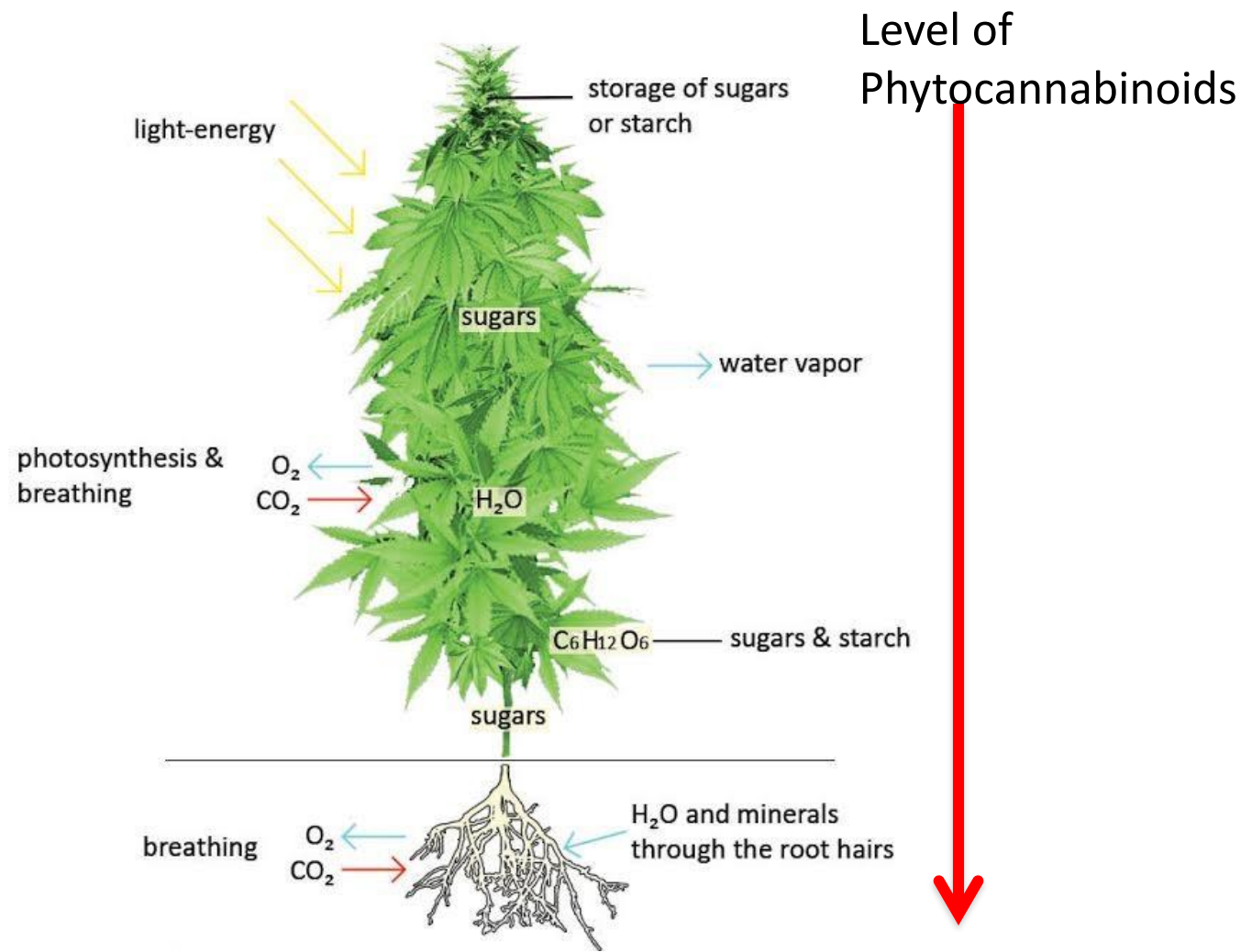
- Does α -Pinene in three hemp cultivars have an inhibitory activity of microbial growth?
- Yes, results demonstrate α -Pinene (in hemp essential oils) significantly inhibits microbial growth
 - Gram (+ and -) bacteria
 - Yeasts
- Conclusion: industrial hemp essential oils applications could control spoilage, food-borne pathogens, and phytopathogen microorganisms.

Cannabis chemicals

	Boiling point	Partition Coefficient, logP
Myrcene	166 ° C (330 ° F)	4.30
Limonene	176 ° C (349 ° F)	3.40
Linalool	198 ° C (388 ° F)	2.65
α-Pinene	155 ° C (311 ° F)	2.80
Geraniol	230 ° C (446 ° F)	3.28
THC	157 ° C (315 ° F)	6.97
CBD	180 ° C (356 ° F)	6.33
CBN	185 ° C (365 ° F)	6.93

Cannabis chemicals

Why does Cannabis produce Phytocannabinoids?



Cannabis chemicals

Why does *Cannabis* produce Phytocannabinoids? What we know....

Plant organ matters!

Highest amount of THC & CBD is found in flower (Andre et al., 2016)

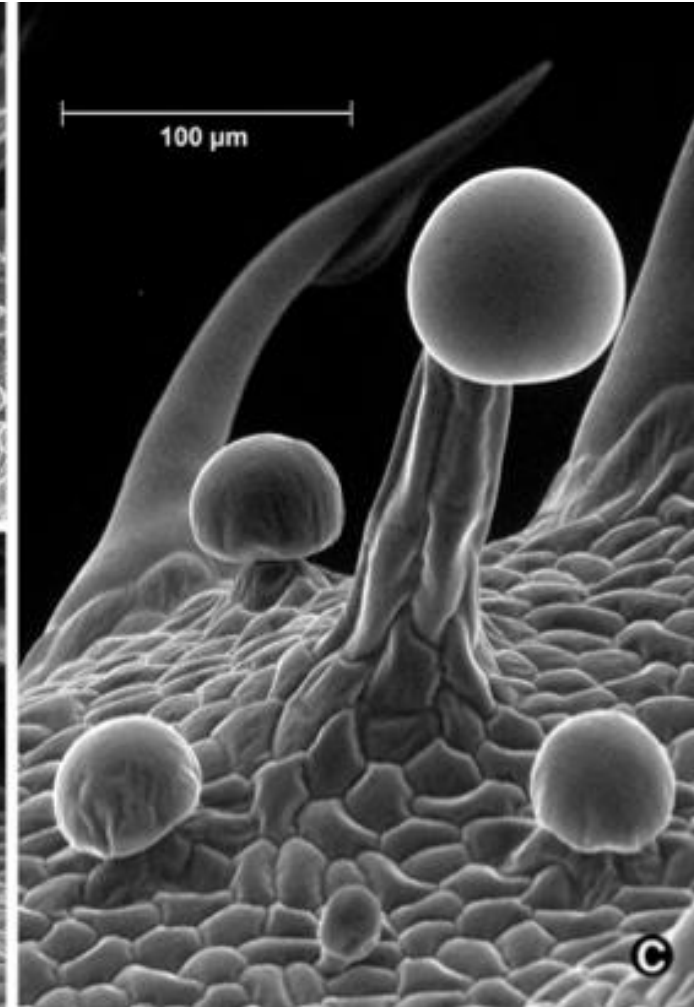
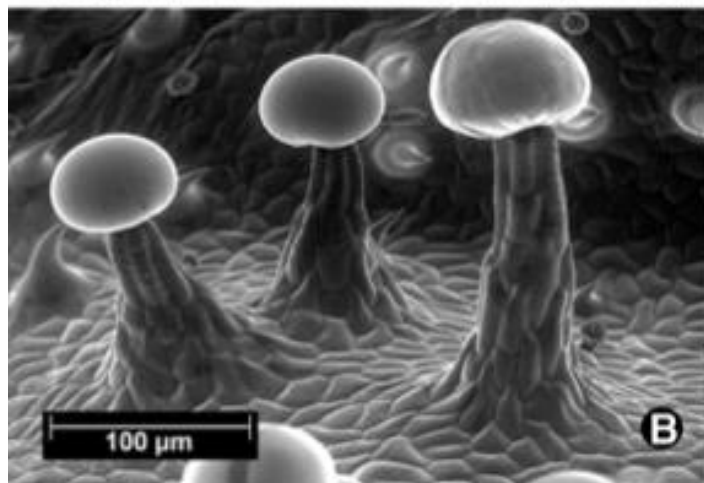
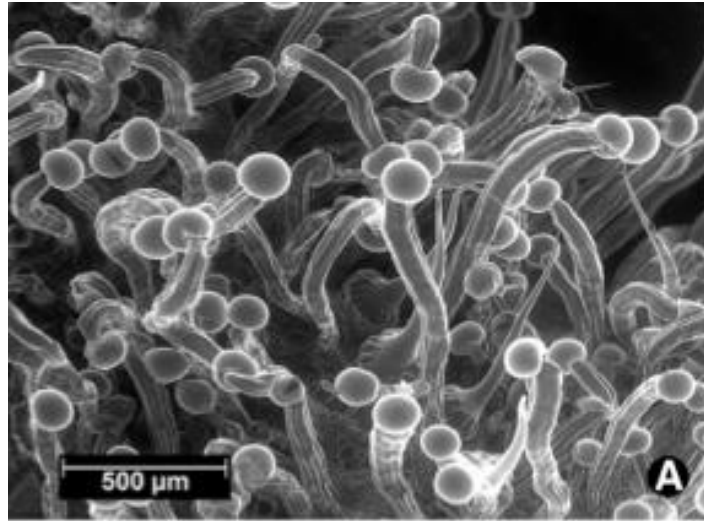
Molecules	Hairy roots	Root		Seed		Stem		Leaves		Pollen		Flower	
		Fiber-type	Drug-type	Fiber-type	Drug-type	Fiber-type	Drug-type	Fiber-type	Drug-type	Fiber-type	Drug-type	Fiber-type	Drug-type
THC	1.04 ^a			0-12 (<0.5 in kernel) ^c 3-29 ^d	36-174 (<2 in kernel) ^c 15-70 ^d	196-475 ^j	3000 ^e	2000 ^f	60300 ^g 22000 ^f 8000 ^e		31230 ^h	76300 ⁱ	95100 ^g 34000-200000 ⁱ 152000 ^e
CBD	1.67 ^a	14.3 ^b		67-244 ^d	4.2-78 ^d	179 ^b 7850-18090 ^j		1790 ^b 20000 ^f	11200 ^g 3000 ^f		440 ^h	8590 ^b 6000 ⁱ	10900 ^g <600 ⁱ
CBN				2-7 ^d	3.4-8.4 ^d	0-47 ^j			800 ^g		1350 ^h		600 ^g
CBG	1.63 ^a							2000 ^f	1000 ^f		1310 ^h	<600 ⁱ	1000-10000 ⁱ
THCV											510 ^h	<600 ⁱ	(<600) - 1300 ⁱ
CBC											3240 ^h	4 600 ⁱ	900-2200 ⁱ

Cannabis chemicals

Why does *Cannabis* produce Phytocannabinoids? What we know....

Size matters!

The amount of THC is correlated to the size of resin gland (Small and Naraine, 2015)



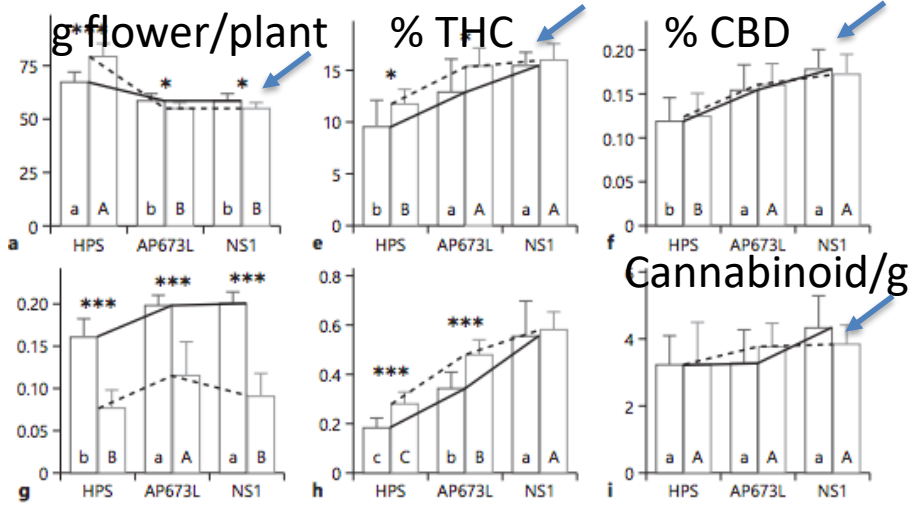
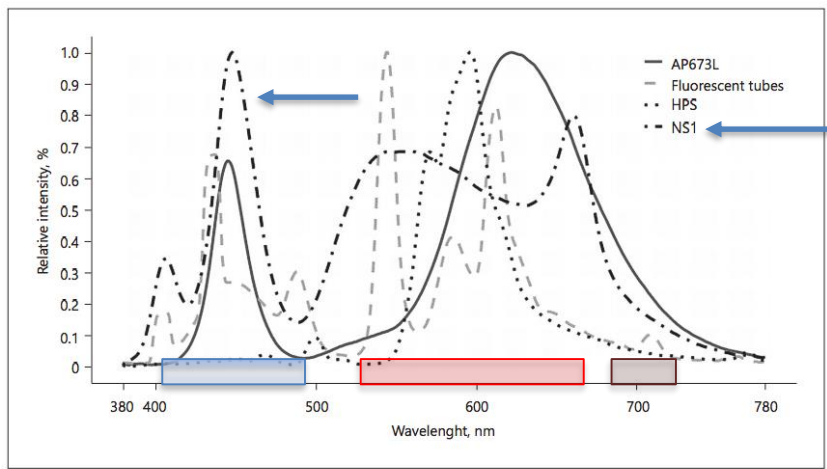
Cannabis chemicals

Why does Cannabis produce Phytocannabinoids? What we know....

Light quality matters!

- Magagnini et al. (2018)
Phytocannabinoid yield changes with different light sources
 - Perhaps complex mechanisms mediated by the UV-A and blue wavelengths that induce CBG accumulation (CBG is precursor of other phytocannabinoids)

- Lydon et al. (1987) In “drug-type” plants, increasing levels of UV-B radiation corresponded with increased levels of THC
 - Potential for selective pressure to favor “drug-type” plants in environments with high levels of UV radiation



Cannabis chemicals

Why does Cannabis produce Phytocannabinoids?

Desiccation Prevention?

- Major Phytocannabinoids increased when intentional drought applied seven weeks into reproductive stage (Caplan, 2018)

- Wild plants in cool humid environments had fewer glandular hair compared to plants in hot dry environments (Sharma, 1975)

- Higher THC levels measured in drier continental climate compared to maritime climate (Murari et al., 1983)

Treatment	Yield	THC	THCA	CBD	CBDA
				Concentration (%) ^z	
Control	-	0.3 ± 0.02	4.7 ± 0.03	0.2 ± 0.01	9.1 ± 0.05
Drought	-	0.3 ± 0.01	5.3 ± 0.09	0.2 ± 0.01	10.3 ± 0.09
Significance ^x	-	NS	**	NS	**
				Cannabinoid Yield (g·m ⁻²) ^z	
Control	164 ± 8.5	0.4 ± 0.03	7.7 ± 0.40	0.3 ± 0.02	15 ± 0.7
Drought	211 ± 16.5	0.6 ± 0.07	11 ± 0.9	0.5 ± 0.04	22 ± 1.7
Significance	NS	*	*	*	*

Caplan, 2018

	Hot and dry	Cool and humid
Population	A	B
Stomatal frequency ²	48.9±1.98	27.1±0.33
Trichomes		
Density/cm ² U*	63.8±1.20	28.3±2.20
L**	253.6±4.3	133.6±3.70
Length (µm) U	70.9±0.94	47.3±0.80
L	134.1±3.27	112.1±2.15
Central leaflet		
Length (cm)	8.4±0.11	10.8±0.20
Leaf color	dull green	bright green

¹ The values represent means of 20 measurements ± standard error of the mean. All data are of statistical significance (P ≤ 0.001) as determined by means of a t-test.
² Mean stomatal frequency = stomata of the lower surface of leaves observed through a 40x objective and 10x ocular (field area = 0.152 mm²).
 U = upper surface of leaf.
 L = lower surface of leaf.
 * Cystolith hairs present.
 ** Unicellular pointed trichomes present.

Sharma, 1975

Cannabis chemicals

Why does *Cannabis* produce Phytocannabinoids?

Stress?

- Correlation between low plant height and high Phytocannabinoid content
- Low Mg, higher THC & CBD content

(Coffman and Gentner, 1975)

Table 7. Simple correlations between cannabinoid concentrations and several soil and plant measurements.

Δ^9 THC		CBD		CBC		CBN	
		Soil parameters					
Mg	-0.64*	P ₂ O ₅	-0.64*	Zn	0.84**	Mg/B	0.59*
Ca/Mg	0.74**	Mg	-0.72*	Cu/Zn	-0.78**		
<u>Plant parameters</u>		Ca/Zn	-0.76**	Mg/Zn	-0.67*		
Harvest ht	-0.59*	P ₂ O ₅ /Zn	-0.67*	K ₂ O/Zn	-0.66*		
N (Total)	0.66*	K ₂ O/Fe	-0.69*	K ₂ O/Fe	-0.60*		
Ca/Mg	0.62*	Mg/Cu	-0.64*	K ₂ O/B	-0.67*		
Ca/B	0.64*	Cu/B	0.58*				
Ca/Sr	0.67*	Na/B	0.62*				

*, ** Significant at the 5 and 1% levels, respectively.

Cannabis chemicals

Why does *Cannabis* produce Phytocannabinoids?

Insecticide?

- THC-rich Mexican (vs. CBD-rich Turkish) *Cannabis* was reported fatal to tiger moth (*Arctia caja*) larvae (Rothschild *et al.*, 1977)



Cannabis chemicals

Why does *Cannabis* produce Phytocannabinoids?

Chemical plant defense?

- Cannabis extract inhibited germination of Lettuce (*Lactuca sativa*)

(Mahmoodzadeh et al., 2015)

- Cannabis extract decreased the germination of monocots

(Pedulko, 2014)



Cannabis chemicals

Why does *Cannabis* produce Phytocannabinoids?

Disease prevention?

- Harbor antibiotic properties (ElSohly *et al.* 1982)
- Antibiotic properties assist in the overwintering of seed (Fereny, 1956)

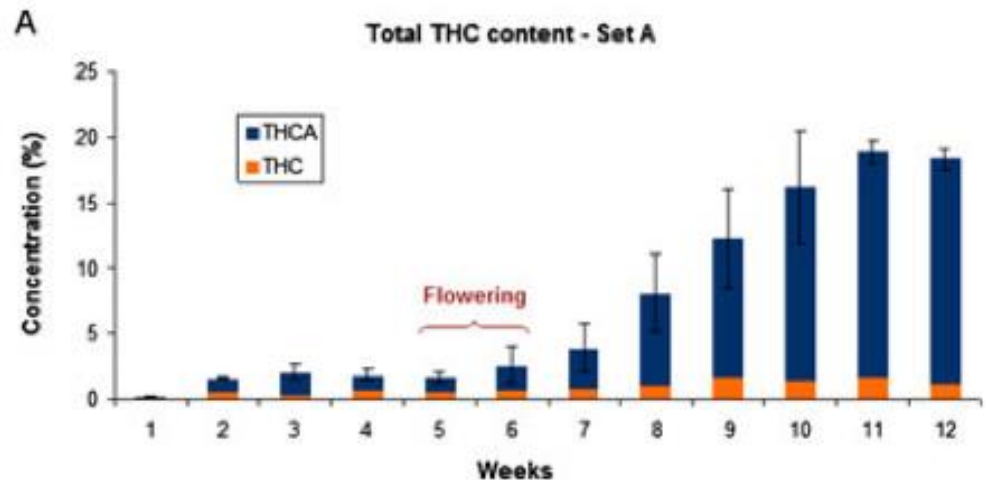


Cannabis chemicals

Why are the amounts of Phytocannabinoids inconsistent?

Plant age changes Phytocannabinoid content

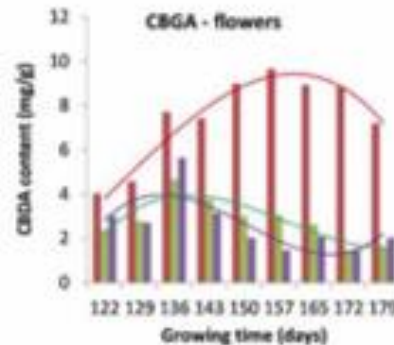
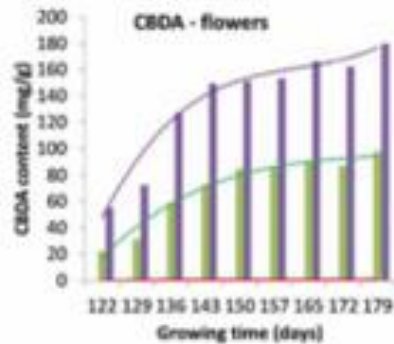
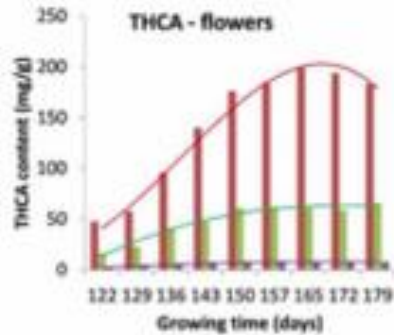
- THC increases throughout the life cycle of *Cannabis* before reaching a plateau (De backer et al., 2012)



<https://www.cannabisreports.com/news/2016/03/07/study-examines-cannabinoid-terpene-development-patterns-three-cannabis-chemotypes/>

Cannabis chemicals

Why are the amounts of Phytocannabinoids inconsistent?



Phytocannabinoid difference due to changes in:

- Genetics
- Plant Organ
- Light
- Soil composition
- Available moisture
- Age

Cannabis chemicals

How is Phytocannabinoid and terpene production related?

- Levels of cannabinoids and terpenoids correspond

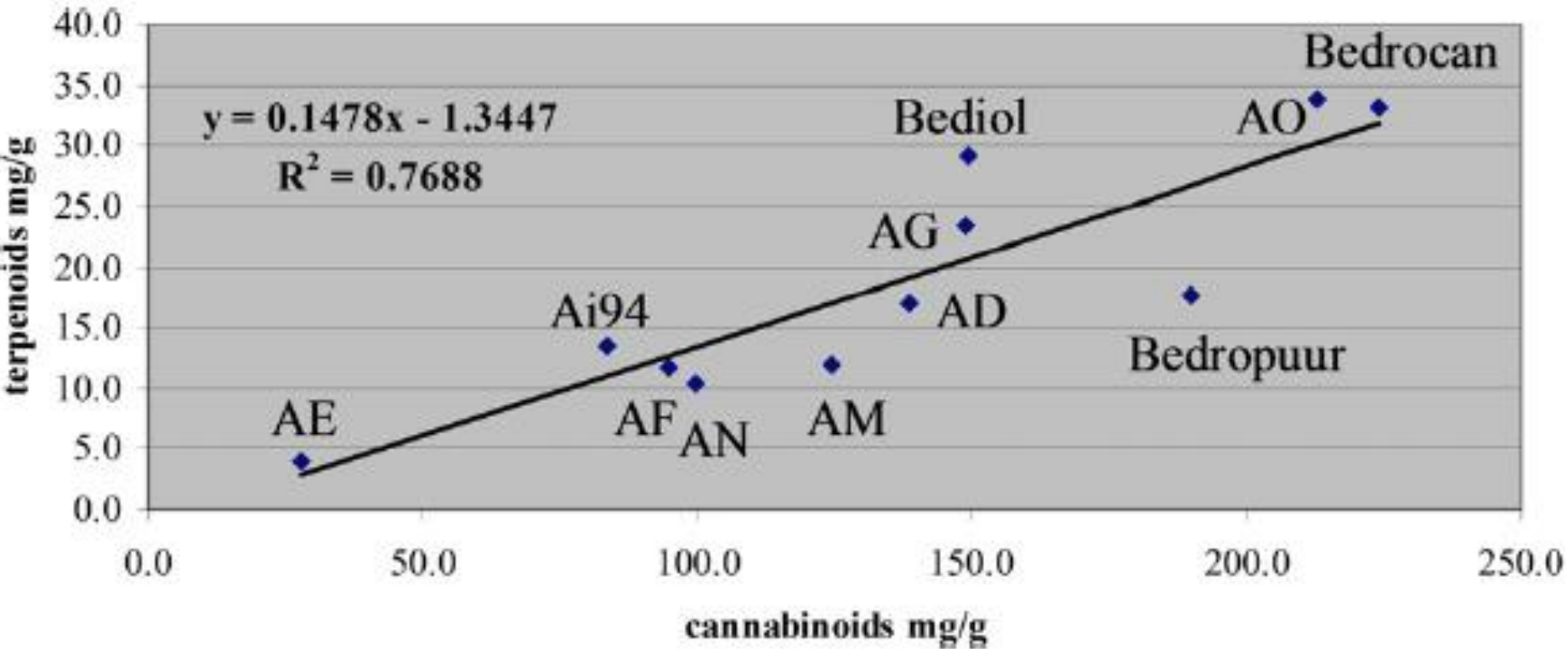
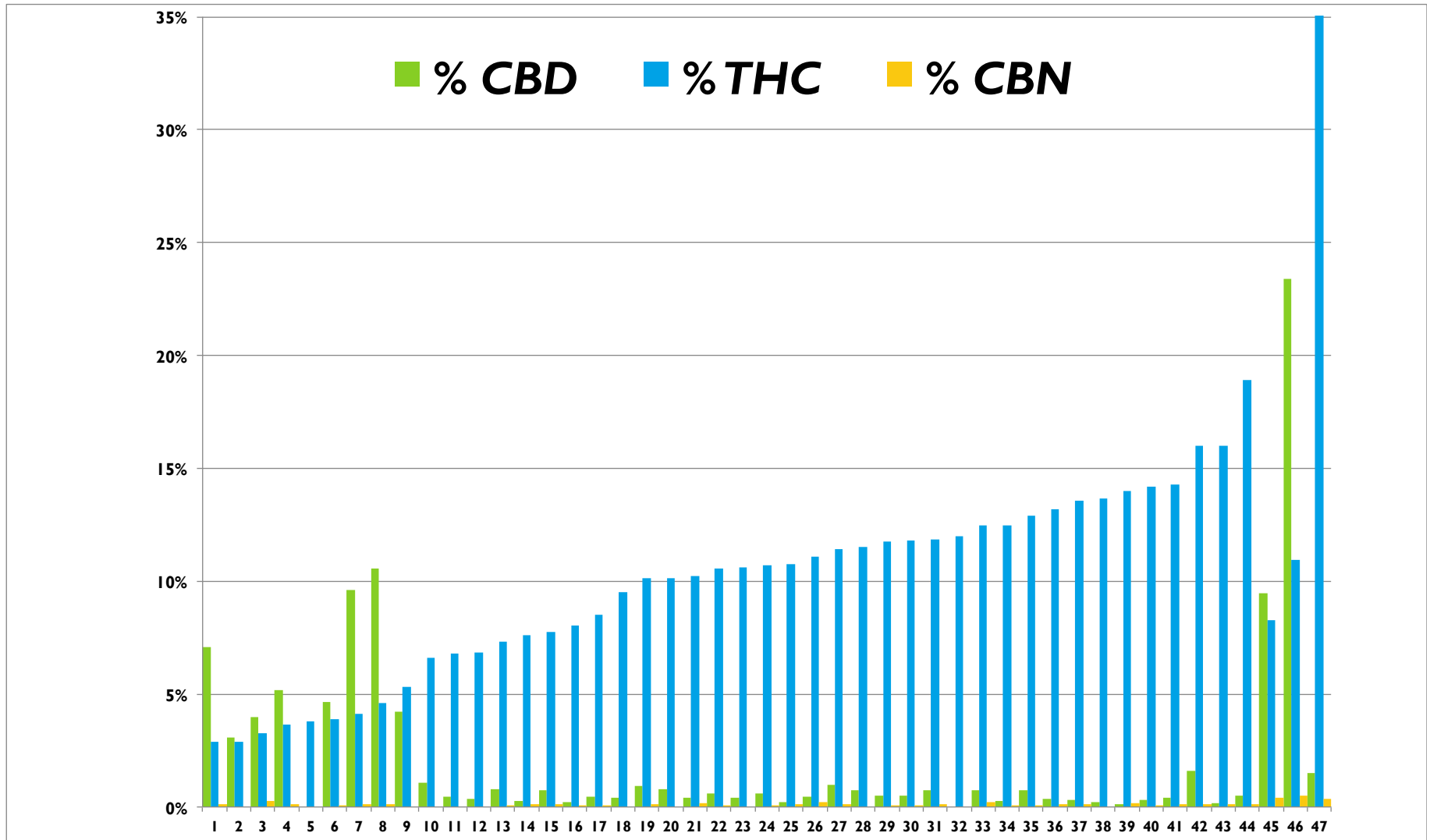


Fig. 1. Correlation of cannabinoid versus terpene levels. (Fischedick et al., 2010)

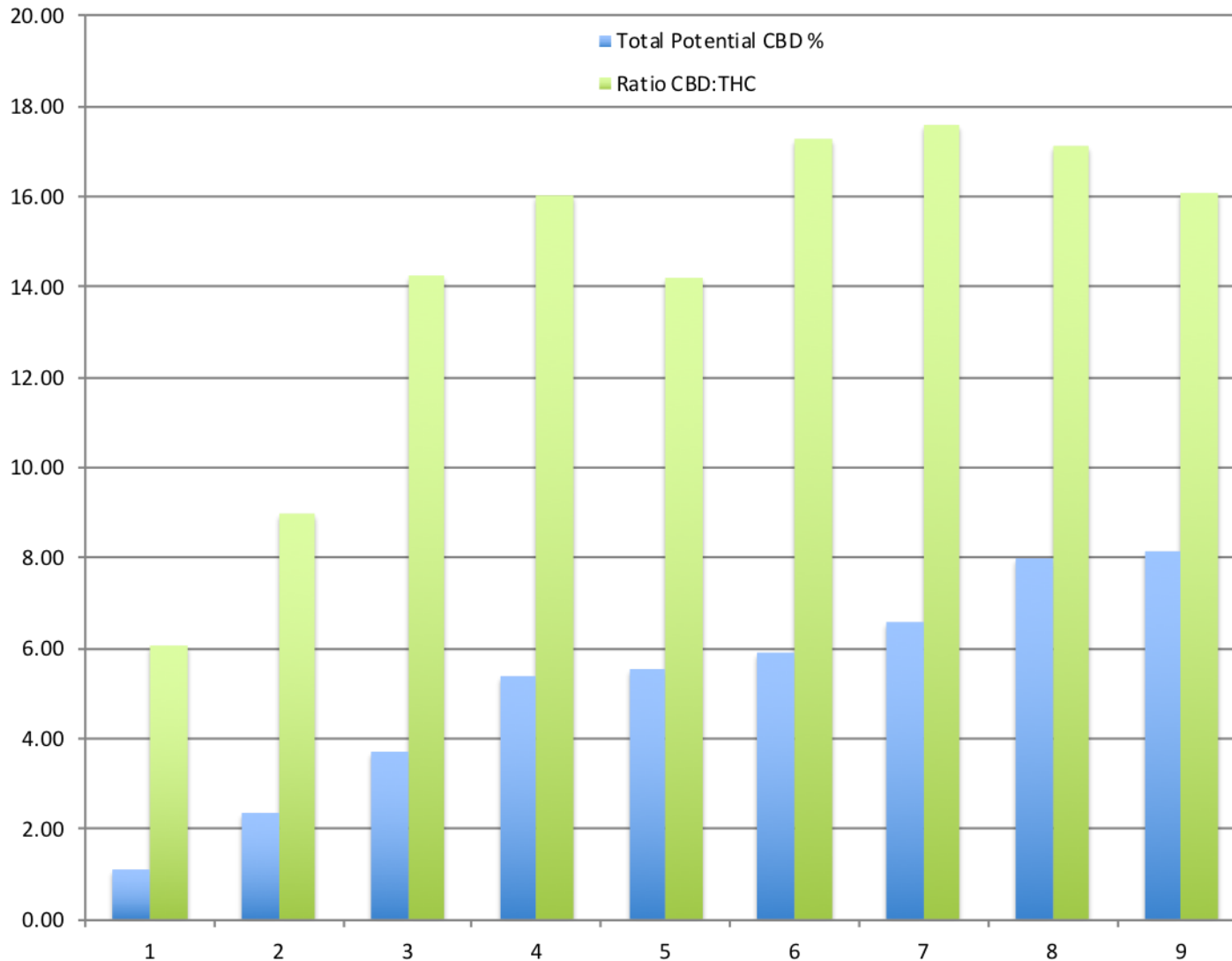
Cannabis chemical research

Are there variations in the chemical composition of *Cannabis* grown under Title 18 of the Vermont Statutes?



Cannabis chemical research

Are there variations in the chemical composition of *Cannabis* grown under the Industrial Hemp Program in Vermont?



Parameters controlled:

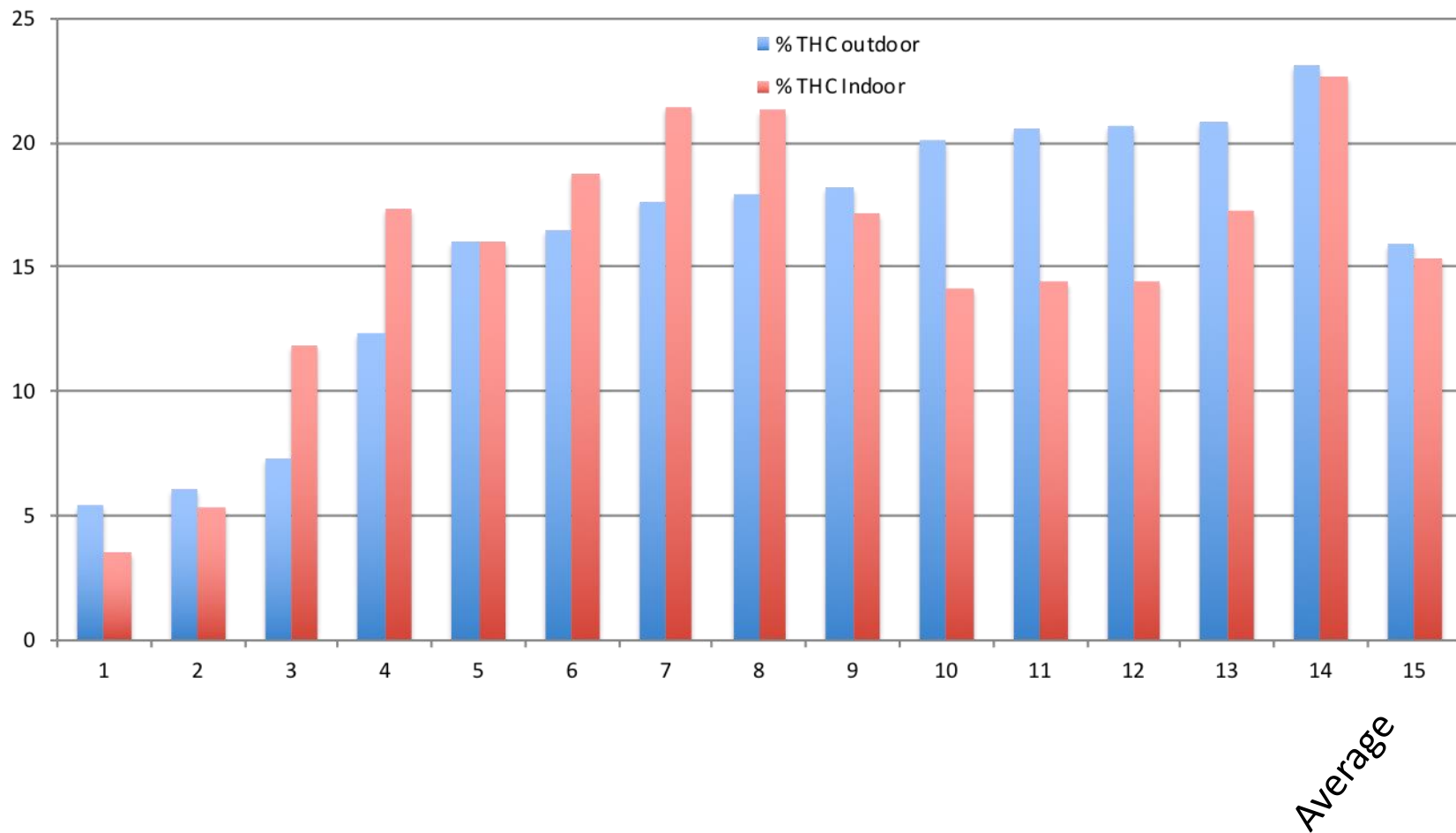
- Organ harvested
- Light
- Soil composition
- Available moisture
- Harvest Age

Variables:

- Genetic composition

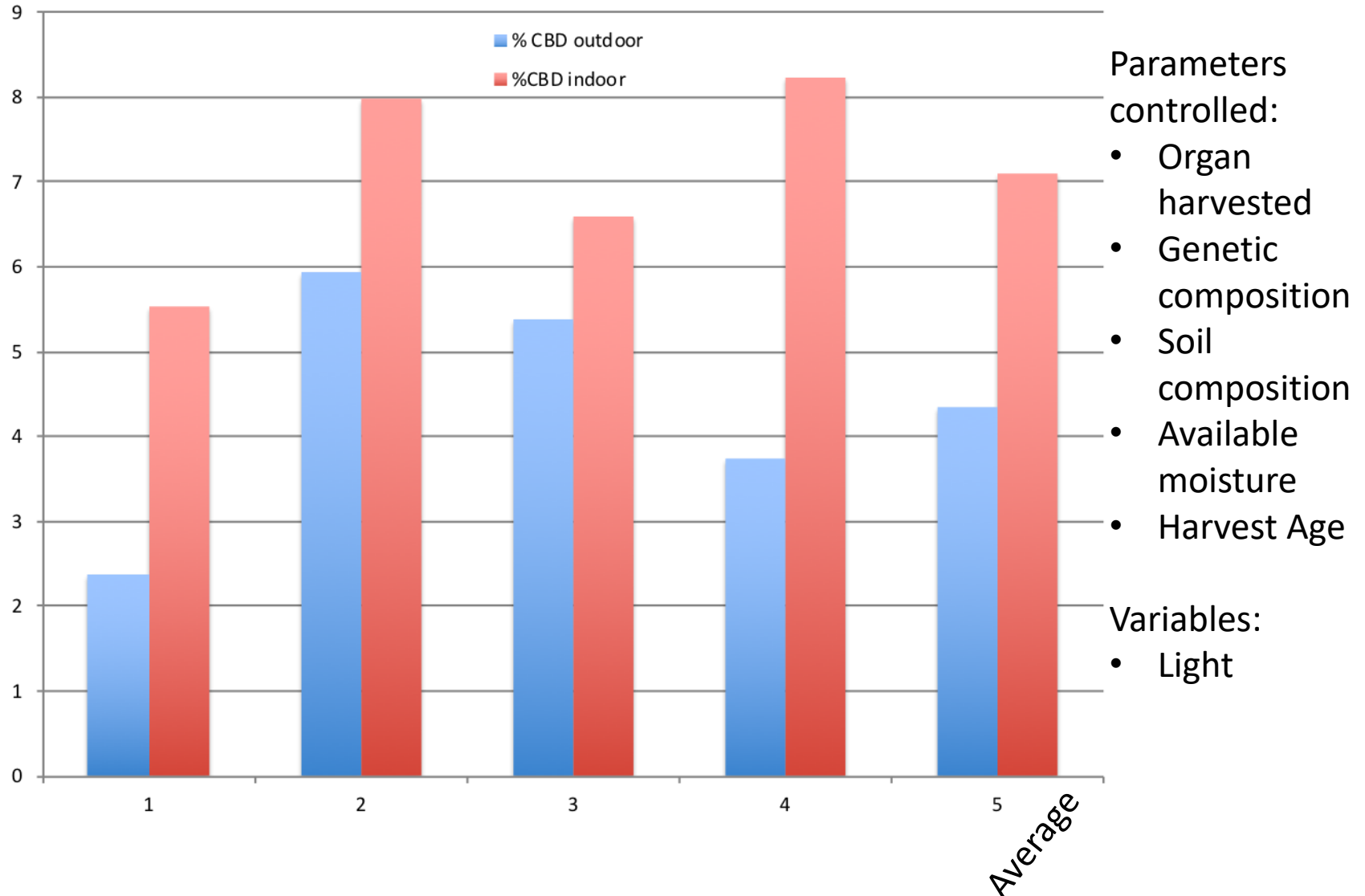
Cannabis chemical research

Are there variations in the chemical composition of *Cannabis* grown in different environmental conditions under Title 18 of the Vermont Statutes?



Cannabis chemical research

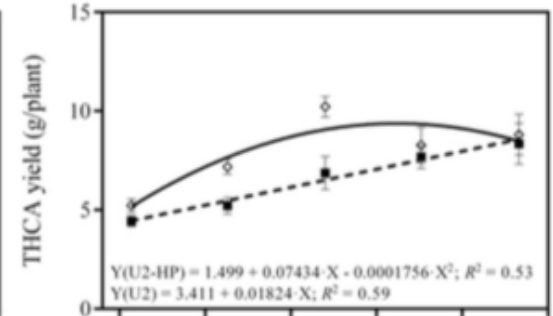
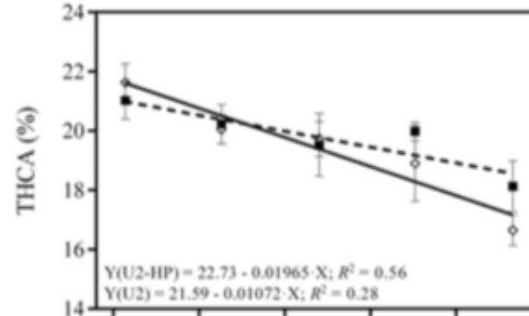
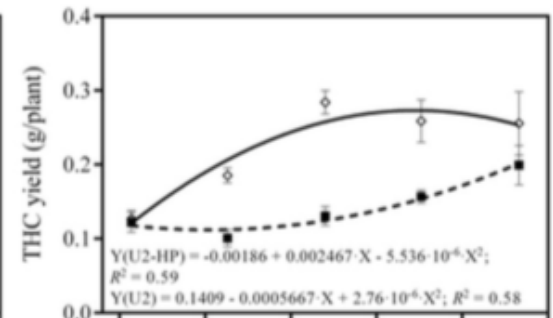
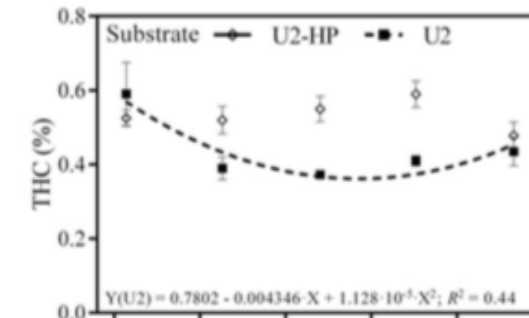
Are there variations in the chemical composition of *Cannabis* grown in different environmental conditions under the Industrial Hemp Program in Vermont?



Cannabis chemical research

Does *Cannabis* grown with different nutrients yield different chemical compositions?

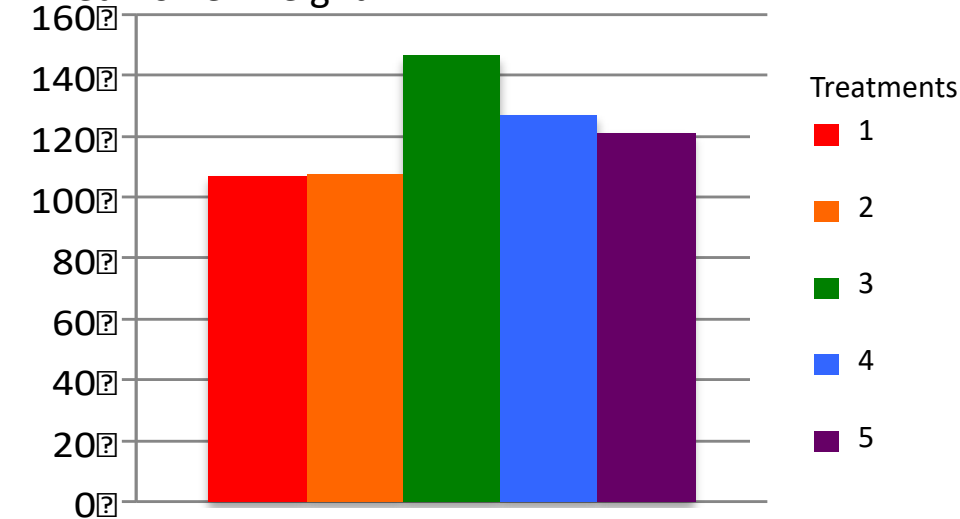
- Different fertilization concentrations produced changes in vegetative growth, biomass yield, and phytocannabinoid concentrations
 - Increasing fertilizer rate had a dilution effect on THC, THCA, and CBGA, despite increased biomass yield (Caplan et al., 2017; doi: 10.21273/HORTSCI12401-17).



Cannabis chemical research

Does *Cannabis* grown with different nutrients yield different chemical compositions?

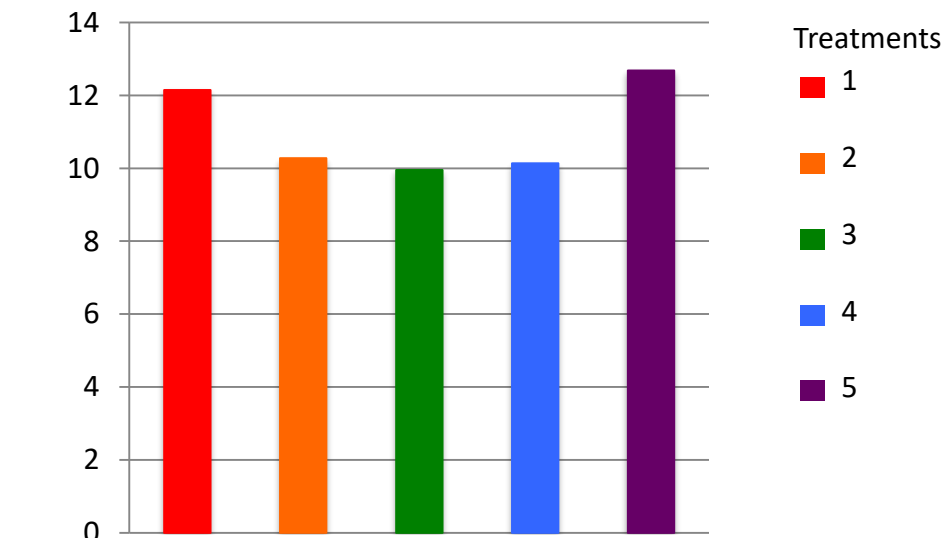
Dried flower weight



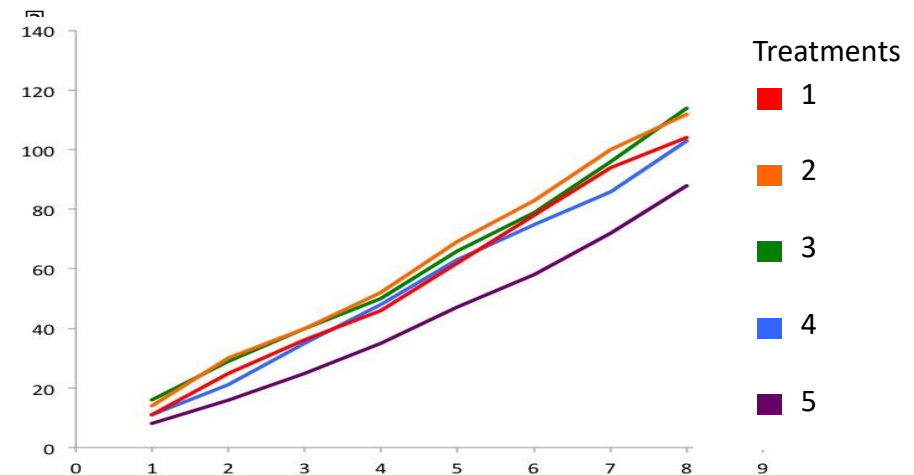
Parameters controlled:

- Organ harvested
- Light
- Available moisture
- Harvest Age
- Genetic composition

Percent Phytocannabinoid by weight



Vegetative growth curve



Cannabis: the name

Taxonomy

- Family: Cannabaceae
- Genus: *Cannabis*
- Species?
 - At least **13** *Cannabis* species have been described



Why is the scientific name important?

Cannabis: the name

Why worry about using a scientific name?

Consistency!

“hemp” usually = *C. sativa*, but the term has been applied to many fiber crops

- Manila hemp = *Musa textilis* (banana anyone?)
- Sisal hemp = *Agave sisalana* (related to tequila!)
- Sunn hemp = *Crotolaria juncea* (pea family)

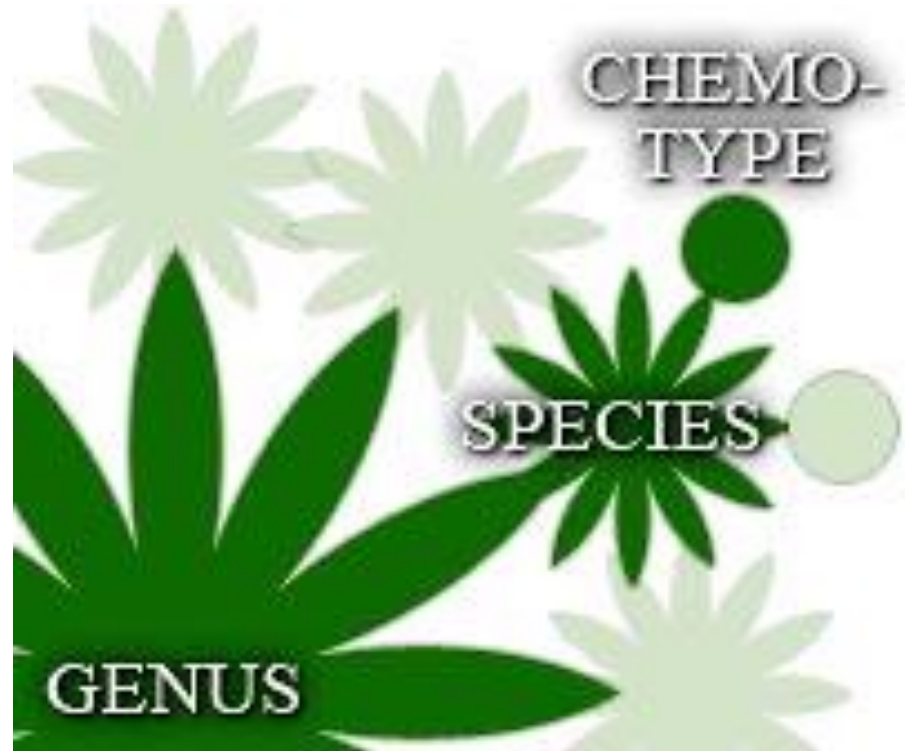


Cannabis: the name

What is the difference between hemp and marijuana?

Chemical content!

< 0.3% THC content = Hemp



- Plants can generate different chemical constituents due to the environment in which they grow
- The different chemical compositions within the same plant species are called chemical phenotypes, or “chemotypes”

Cannabis: the name

Is there a genetic difference between hemp and marijuana?

Cannabis genome and transcriptome

- Published 2011
- Sequenced DNA and RNA with Illumina Next-generation technology
- SNP identified differences in “hemp” and “marijuana genome

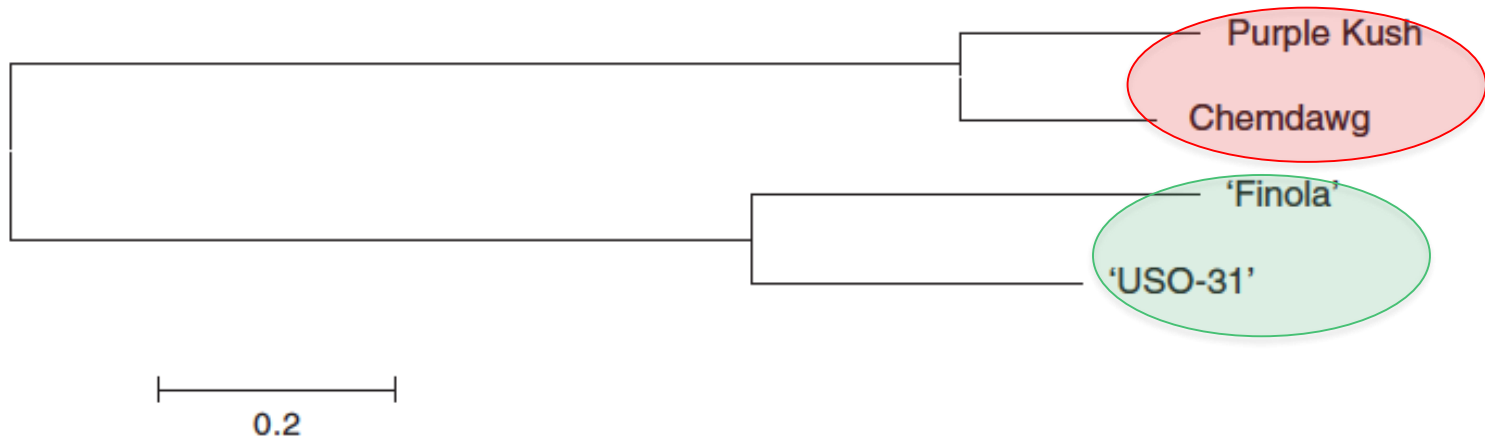
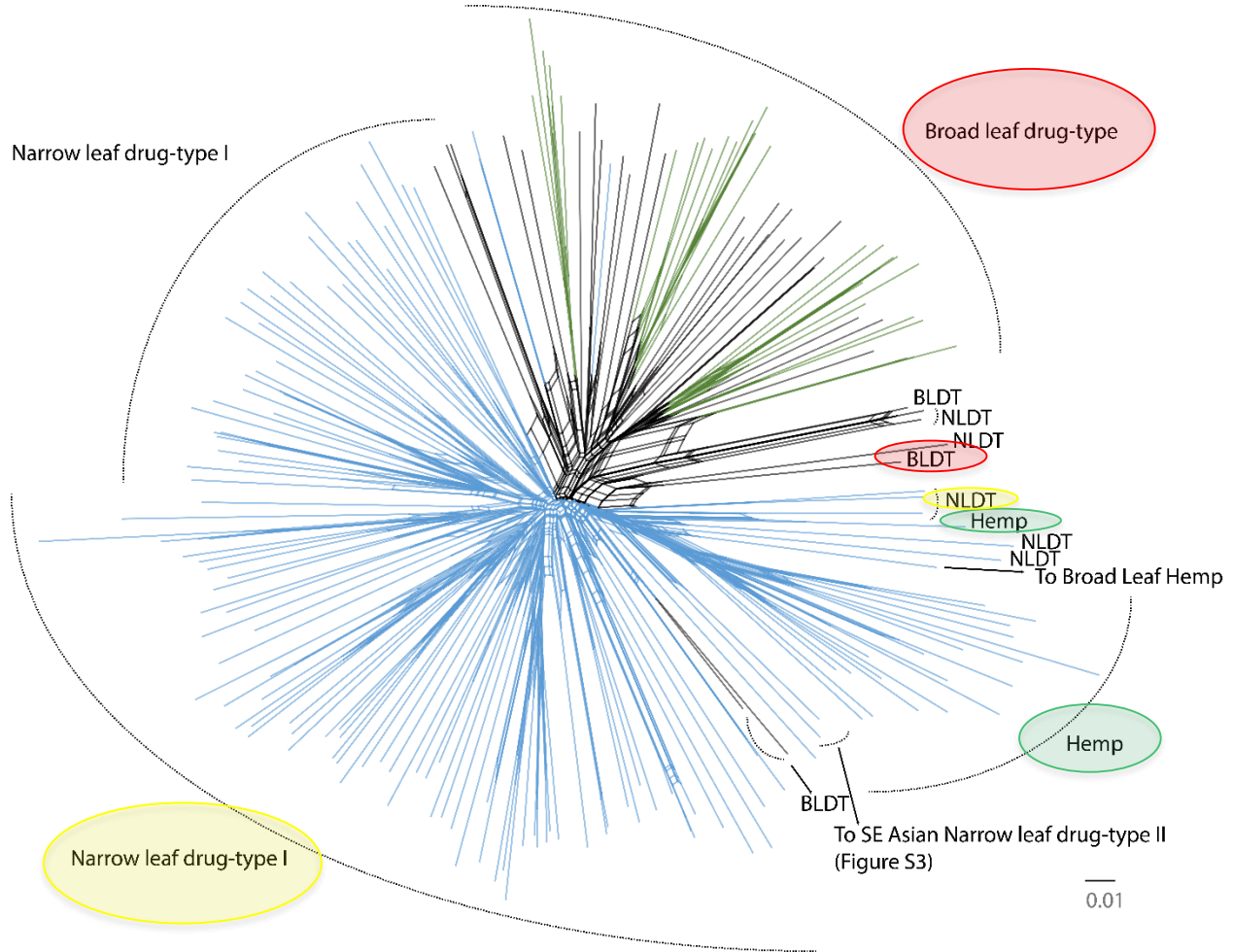


Figure 5 Neighbour-joining tree for two hemp cultivars and two marijuana strains. The tree was plotted in MEGA5 [71] using the maximum composite likelihood of SNV nucleotide substitution rates, calculated based on the concatenated SNV sequences in each variety, as a distance metric. The topology of the tree reveals a distinct separation between the hemp and marijuana strains.

Cannabis: the name

Is there a genetic difference between hemp and marijuana?



Phylogenetic neighbor network of ~3000 SNP alignment from the Cannabis genome

Cannabis: the name

Is there a chemical difference between hemp and marijuana?

Yes, if chemotypes are based on CBD/THC ratio

- Hillig and Mahlberg (2004) suggest distinct groups

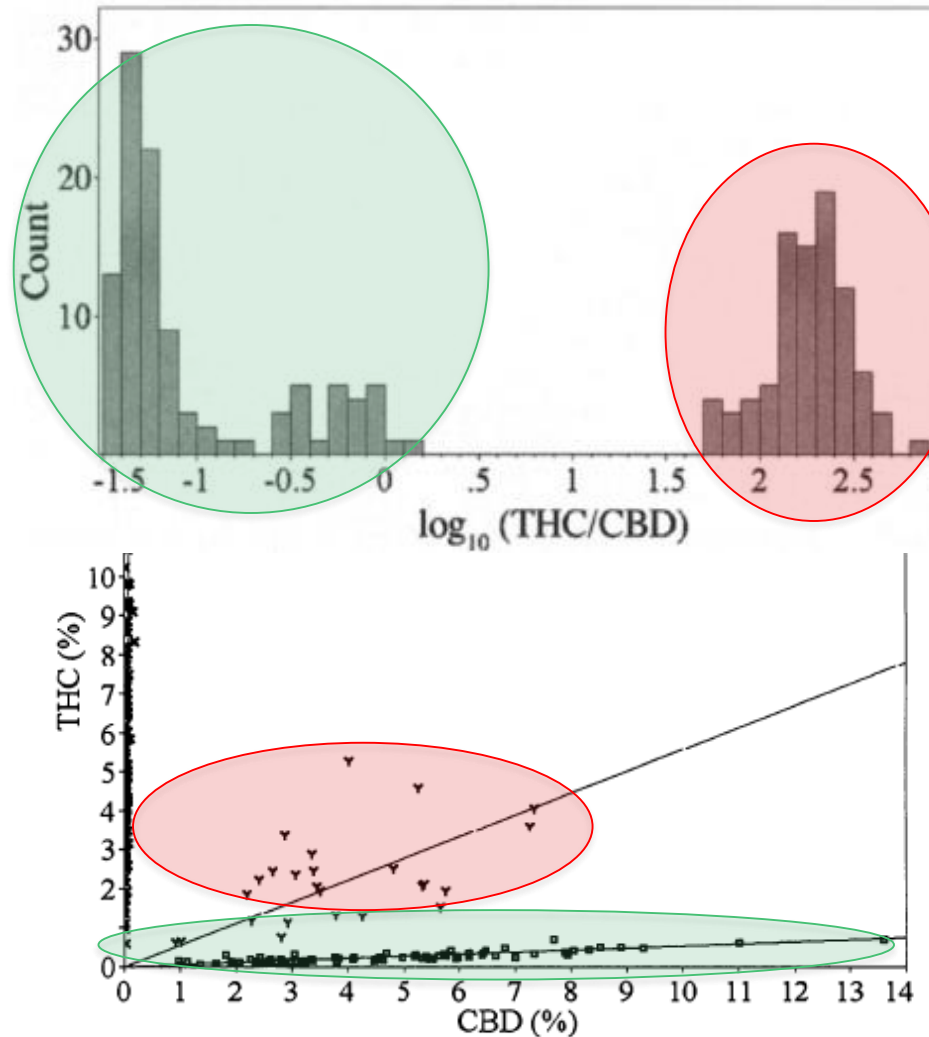
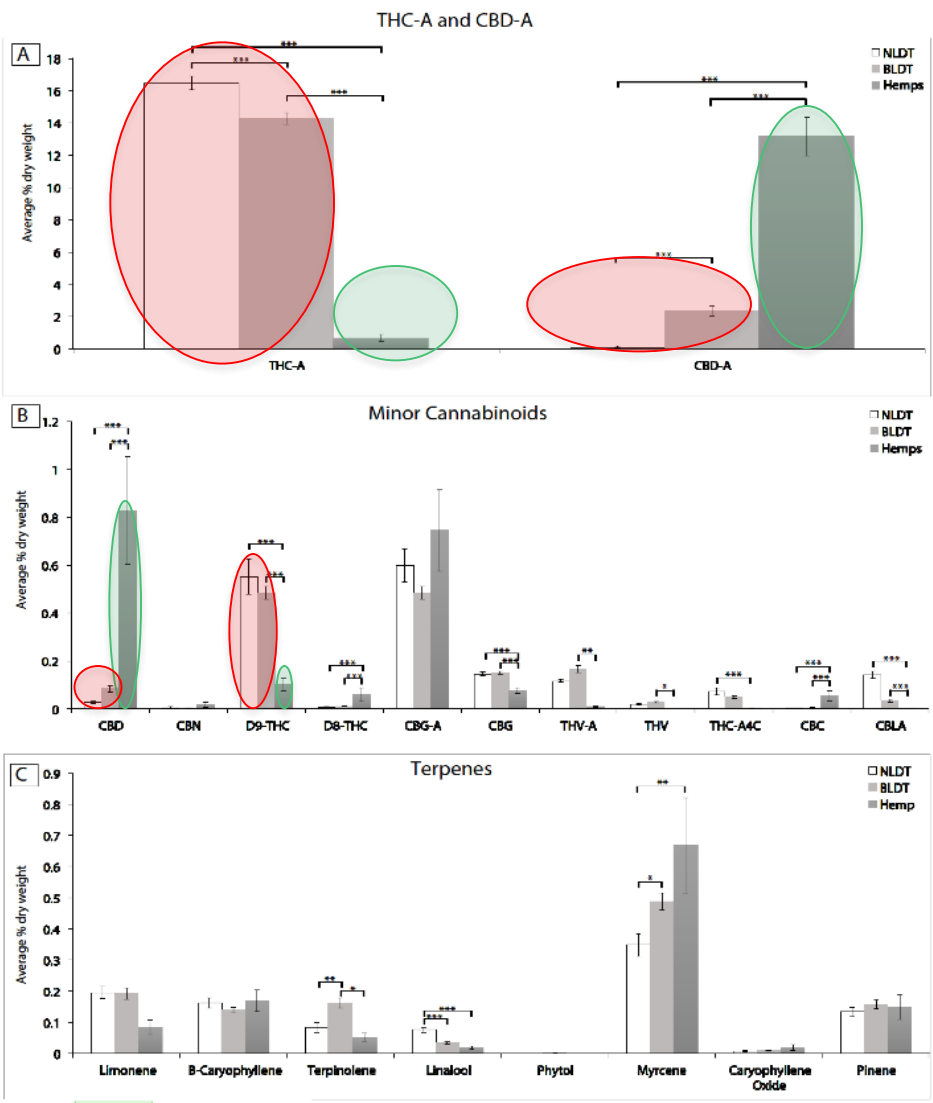


Fig. 4. Plot of Δ^9 -tetrahydrocannabinol (THC) % vs. cannabidiol (CBD) % for 253 *Cannabis* plants. Chemotype I, II, and III plants are marked with an X, Y, and square, respectively. Linear regression lines (forced through the origin) are drawn for each chemotype.

Cannabis: the name

Is there a chemical difference between hemp and marijuana?

Yes, if chemotypes are based on average percentage of major Phytocannabinoid mass for dried and un-pollinated female flowers (Lynch et al., 2015)



Cannabis: the name



Cannabis: the name

Are the drug-type names *Cannabis sativa* and *Cannabis indica* viable?

No, *Cannabis indica* should not be used

- Plants grouped morphologically as *C. indica* (red) or *C. sativa* (blue) do not form distinct groups based on chemical composition
 - one species concept *Cannabis sativa* L.

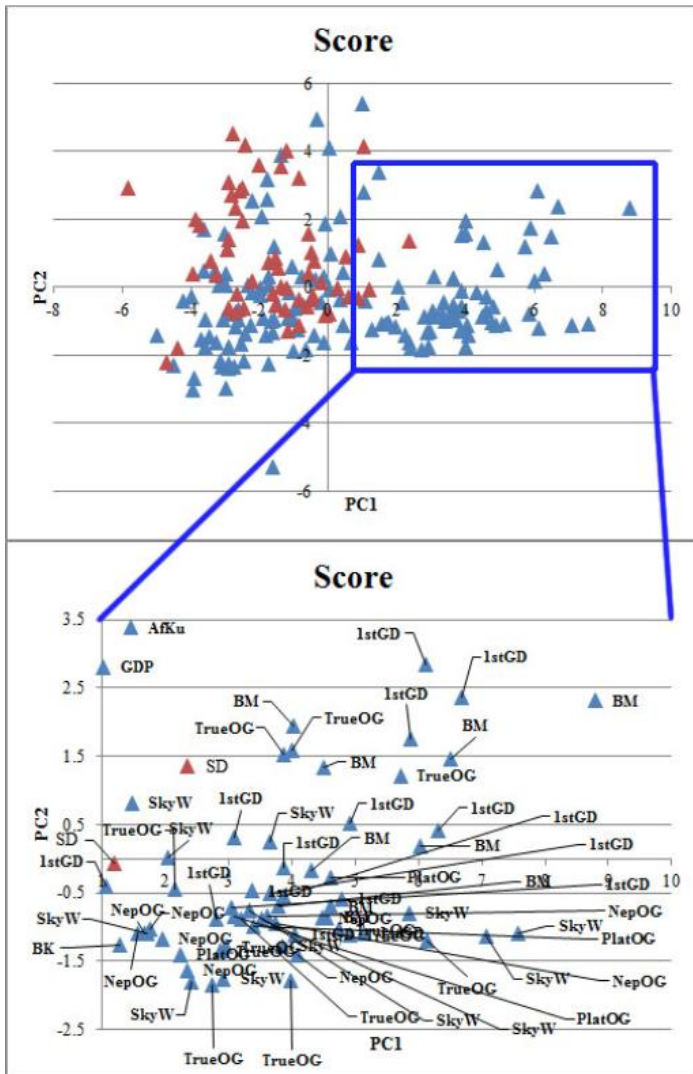


Figure 11: PCA (scaled) scoring plot for indica (blue) and sativa (red).
Ezinga et al. (2015)

Cannabis: the name

Do drug-type *Cannabis* “strains” have different chemotypes?

No, “strains” do not have not consistently reproducible chemical compositions

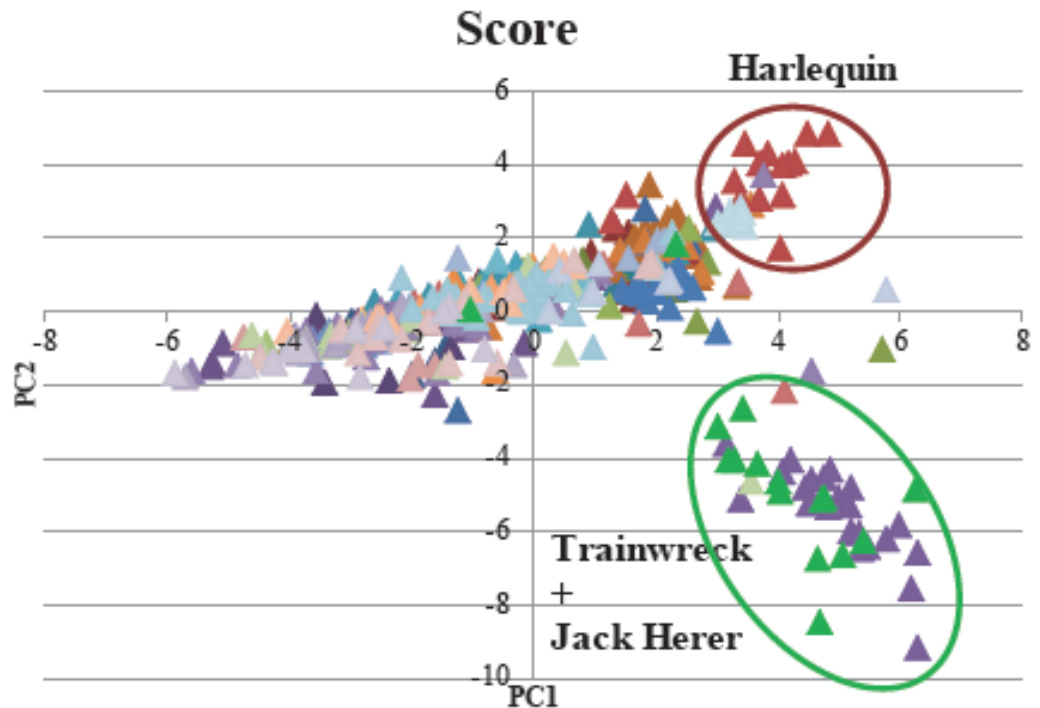


Figure 5: PCA scoring plot of full cannabis flower data set with scaling.

Cannabis names and chemicals

What's Next?

International Code of Nomenclature for Cultivated Plants



- Established in 1953
- Rules
 - Name is unique
 - Follows principle of priority
- Operates within the Botanical code (*International Code of Nomenclature for algae, fungi, and plants*)
- Does not regulate trademarks or marketing names
 - trade designations
 - *Cannabis* “strains” should be identified as cultivars once stabilized

Graduate and Professional Programs



Cannabis Science and Medicine

Translational *Cannabis* Science and Medicine at the University of Vermont College of Medicine Department of Pharmacology

Through education we help turn observations in the laboratory, clinic and community into interventions that improve health and bridge scientific discoveries in medical *Cannabis* with the needs of health care providers, researchers, students, and professionals.

[LEARN MORE !\[\]\(0aff635c4179ba9e710b00f4b01d3b20_img.jpg\)](#)

Why does *Cannabis* impact humans?

Cannabis impacts humans through the endocannabinoid (eCB) system.

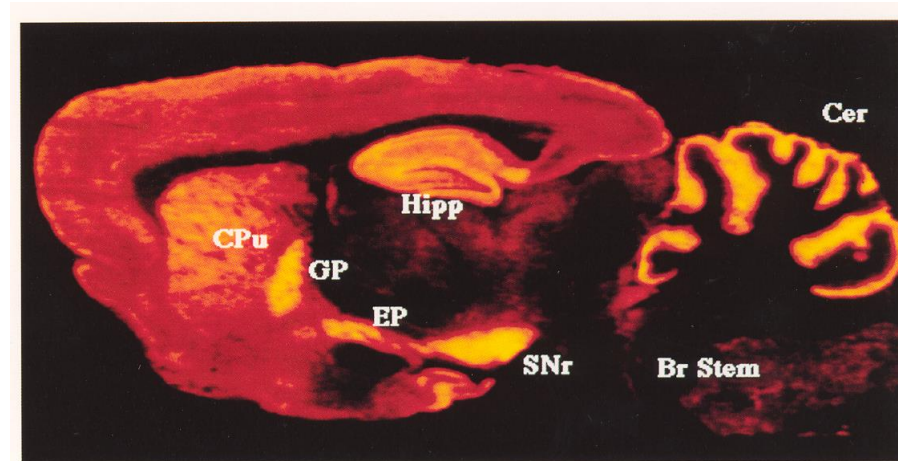
The eCB system consists of:

- cannabinoid receptors (CBs)
- endogenous agonists
- agonist-metabolizing enzymes






Why does *Cannabis* impact humans?

- CB₁ is primarily expressed in neurons
- CB₁ is found in adipose tissue, blood vessels, gut, testes, uterus
- CB₁ is *not found* in the brainstem's cardiorespiratory drive centers – which explains the lack of lethal overdoses from cannabis
 - Unlike opioid receptor distribution



Autoradiograph of rat brain exposed to [³H]CP55,940 (Herkenham *et al.*, 1990).

-  = highest densities in memory centers, limbic system, basal ganglia, cerebellum
-  = lower densities in cerebral cortex
-  = lowest densities in the brain stem

CB₂ is primarily expressed in the immune system

Cannabis clinical research

Original Investigation

Cannabinoids for Medical Use A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidtkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358

Methods

- compilation of data from randomized clinical trials (RCTs) comparing cannabinoids to placebo for many conditions
- information about potential for adverse events (AEs) with cannabis

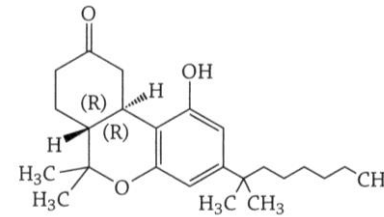
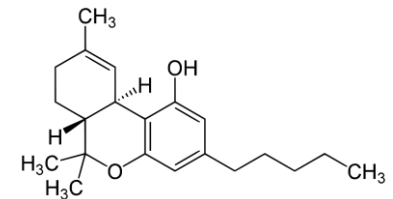
Results

- Improvement in pain when compared to placebo overall (Odds Ratio 1.41 [0.99-2.00])
- Cannabinoids were associated with approximately 3x increased odds of any AE compared to placebo

Cannabis clinical research

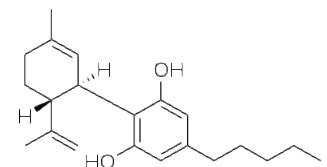
FDA Approved: Synthetic THC

- Dronabinol (Marinol™) for Pain or Nausea
- Nabilone (Cesamet™) for Pain or Nausea



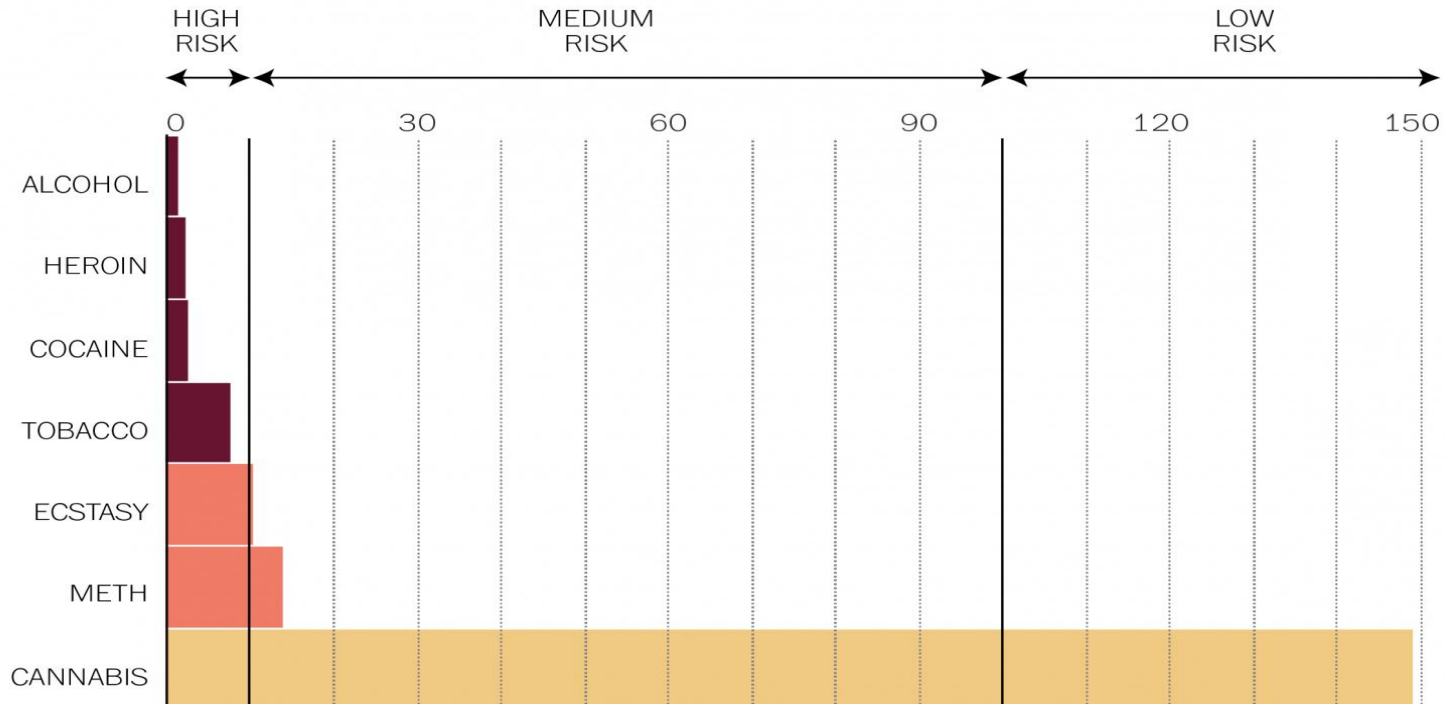
FDA Approved: CBD

- Cannabidiol (Epidiolex®)



Cannabis clinical research

- Risk of pediatric exposure
- Risk of diversion for recreational use
- No known risk of death from the drug itself
 - Margin of exposure (MOE) is the ratio between toxicological threshold (benchmark lethal dose) and estimated human intake based on individual and population scenarios
 - MOE analysis shows that by a wide margin, cannabis is the least risky recreational drug (Lachenmeiera DW and Rehm J., 2015)
Ratio between toxic dose and typical human intake



Cannabis pre-clinical research

Cannabidiol (CBD) activates non-endocannabinoid receptors

- TRPV1 is found in nervous tissue
- TRPV1 is involved in the feeling of pain
- TRPV1 activity can be decreased with overactivity = desensitization
 - Can lead to analgesic effects



Cannabis clinical research

Why not just pharmaceutical products?

1. Dronabinol not well tolerated, Epidiolex just became available, and Sativex is not yet approved in USA
2. When approved, costs could be exorbitant
3. “Whole plant” or “Full spectrum” extracts have other cannabinoids and terpenes with effects on CB receptors



Are plant-based products more effective (and less expensive) than pharmaceuticals?



Can they be provided in a safe and consistent fashion?

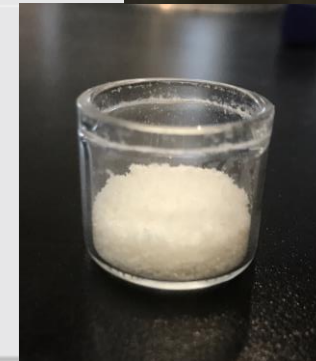
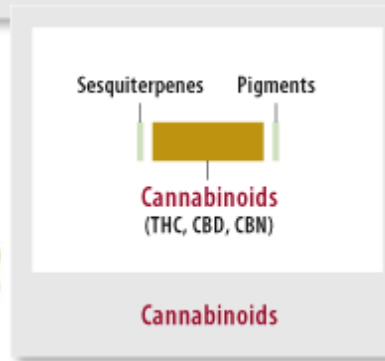
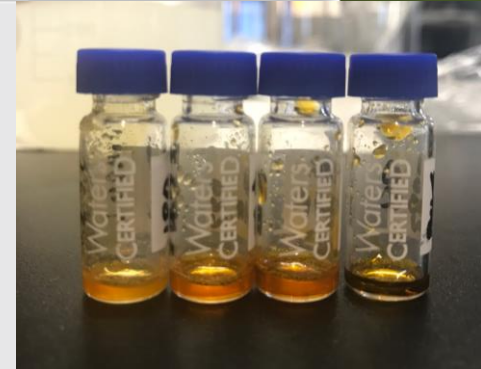
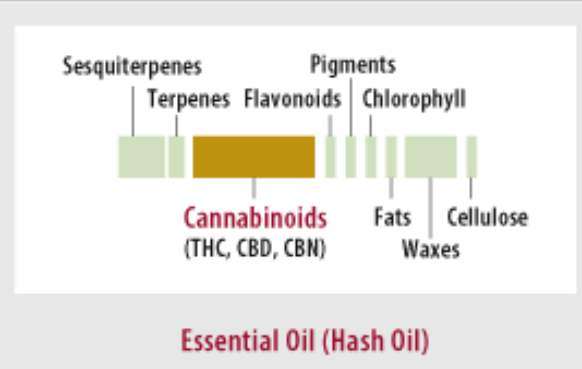
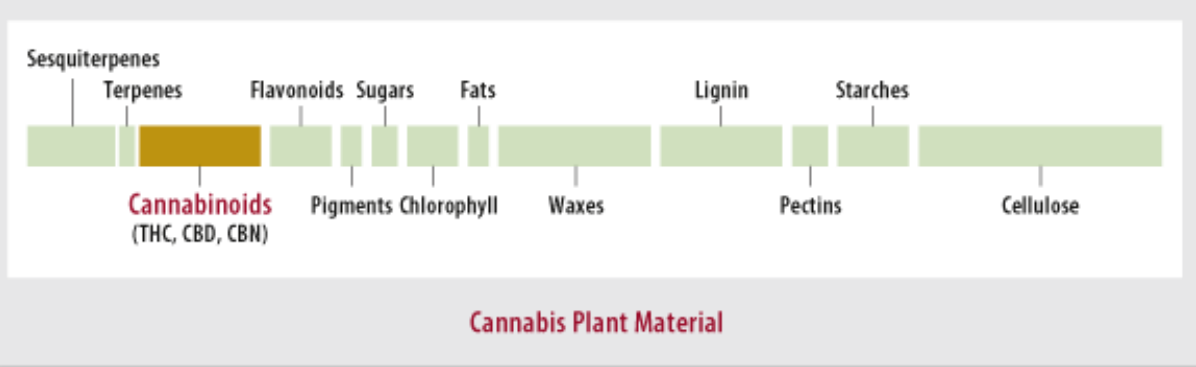
Cannabis research

Label accuracy on CBD products



Cannabis research

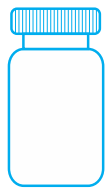
Label accuracy on CBD products



Cannabis research

Label accuracy on CBD

- All products contain CBD!
- Only one product had levels above 0.3% THC
- 50% of products were labeled accurately
- 17% of Vermont products were labeled accurately



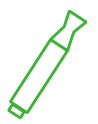
capsules
n=7
dose range: 5-30mg
mean: 13.4mg



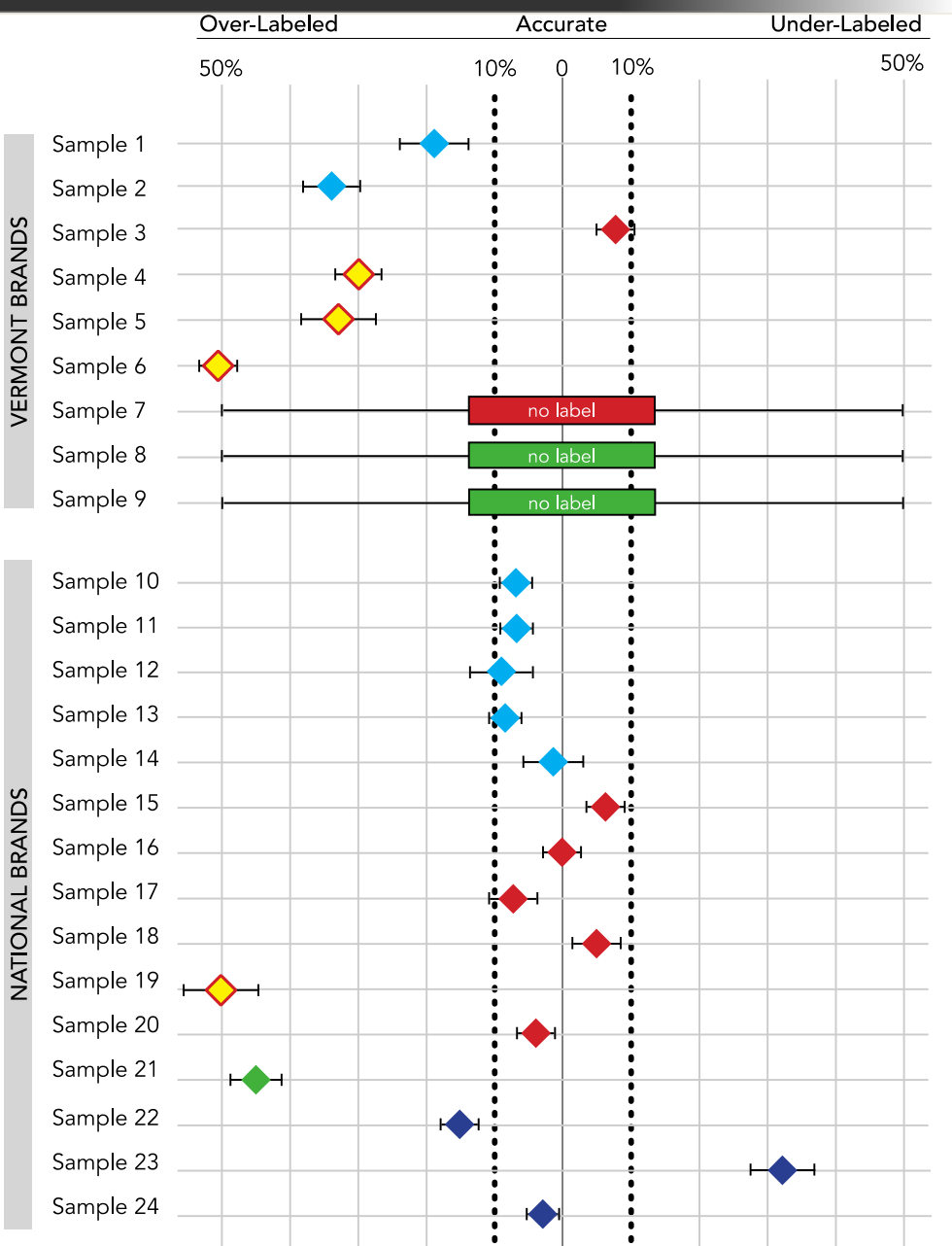
tinctures
n=11
dose range: 1-25mg
mean: 12.9mg



concentrates
n=3
dose range: unlabeled
% potency range: 47.99-77.07%
mean: 63.81%



cartridges
n=3
dose range: unlabeled
% potency range: 14-64%
mean: 32%



Questions?

