NATIVE NATION EVENTS

The Issue of Cannabis Dose

John S Abrams, PhD

Medical Cannabis: The Science, Politics and Legality All In One

Third Native American Cannabis Conference
December 5, 2016

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Overview of Presentation

I. How do we determine cannabis dose?
   - The CESC & The Dosing Project

II. Chemotyping – A better scheme for cannabis product classification than C. *sativa* vs. C. *indica*
   - PhytoCannabinoids
   - Terpenoids

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To Provide Accurate Dosing Guidelines for Cannabis Use

Why The Dosing Project Is Needed

We have launched a web-based, crowd-sourced observational study designed to establish baseline dosing standards

Use initial results to:

- Establish initial Dose & Mode of Administration (MOA) recommendations
- ID commercially viable indications at today's COGs
- Provide guidance for patients as well as Manufacturers & Dispensaries

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The Dosing Project: Background

- Prohibition has delayed our understanding of the cannabis plant and it's effect on the human Endocannabinoid system.
  - Many patients have already discovered through trial and error how to use cannabis effectively for multiple indications
  - There are many other people that would benefit from collective knowledge

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The Dosing Project: Background II

- The Dosing Project is a web-based, crowd-sourced survey that rapidly determines dose in milligrams(mg) and milligrams per kilogram (mpk)

- Observational studies are easily performed in a restrictive research environment

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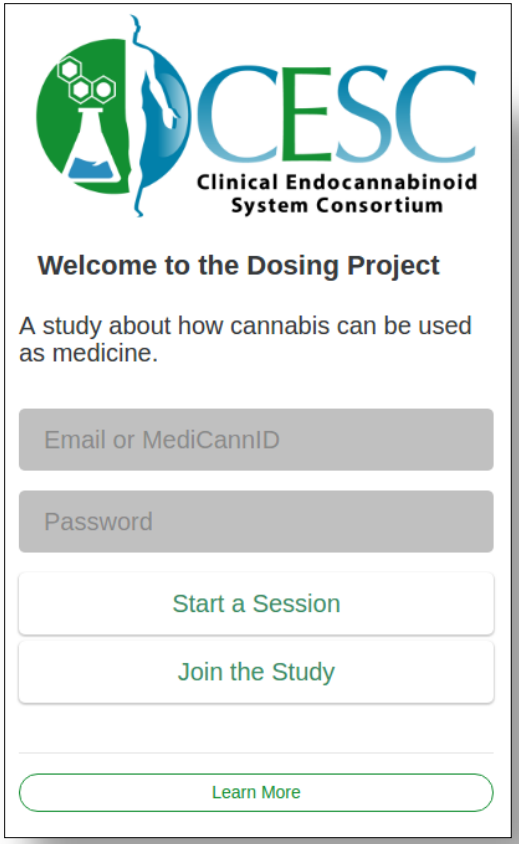

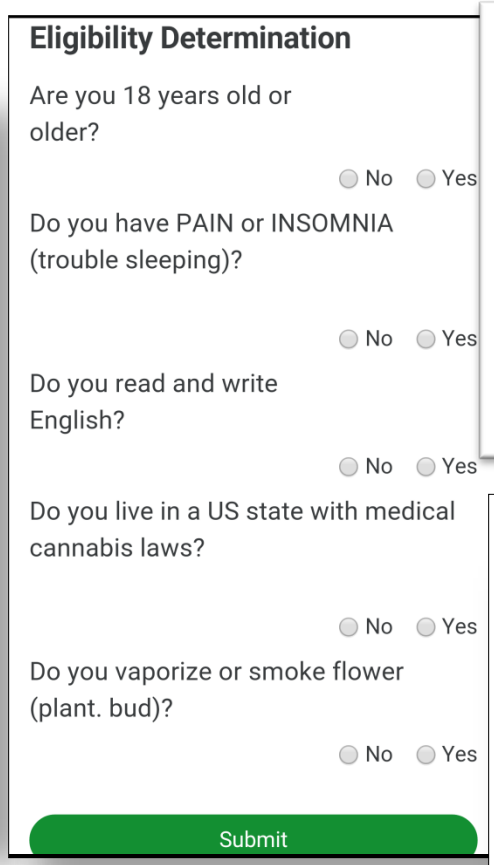

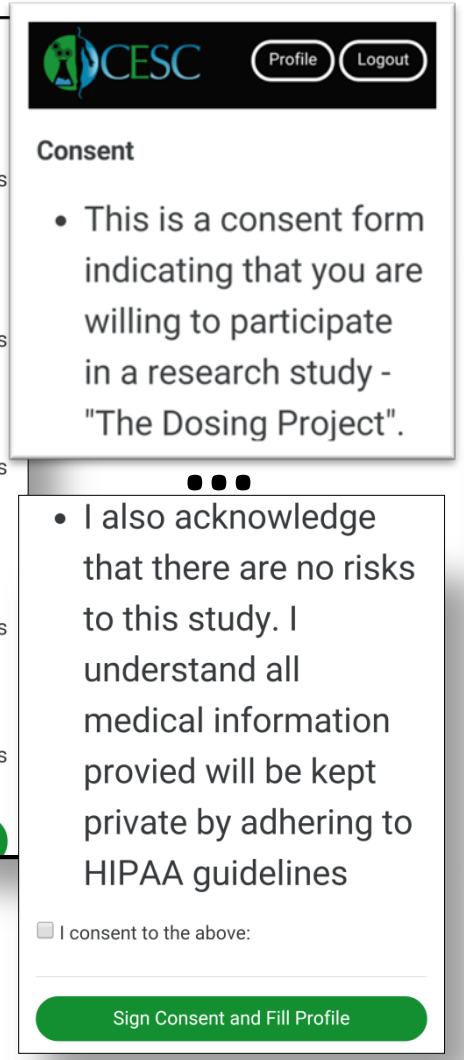

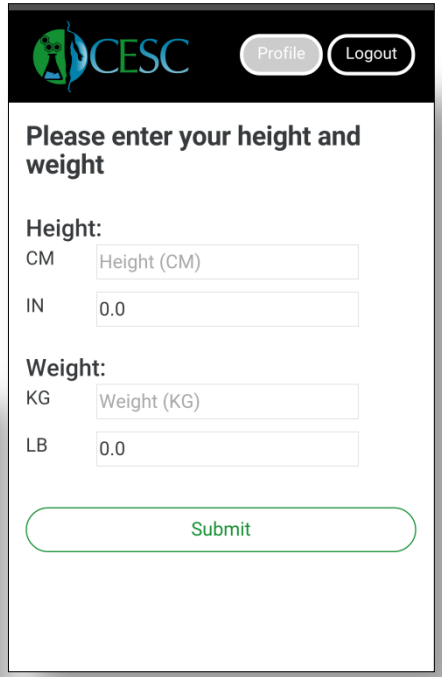

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Profile

Eligibility & Consent Screens

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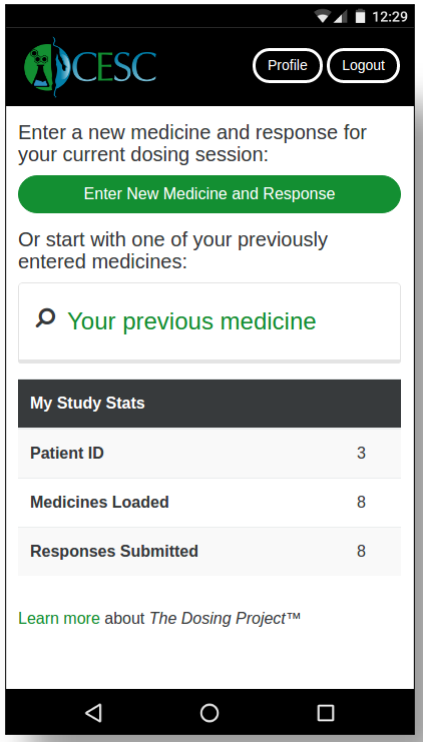

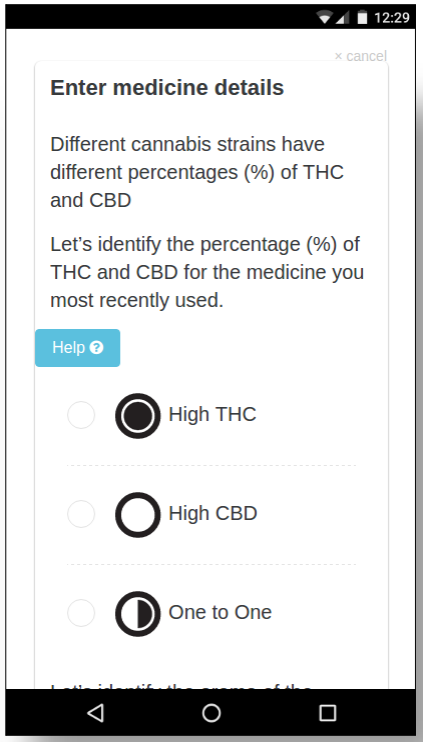

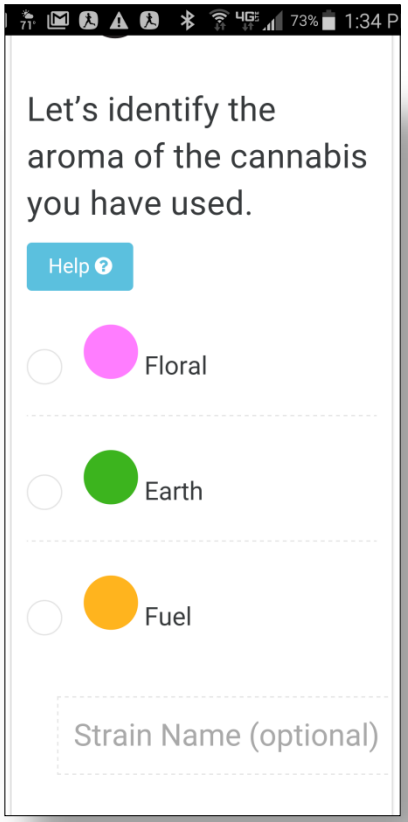

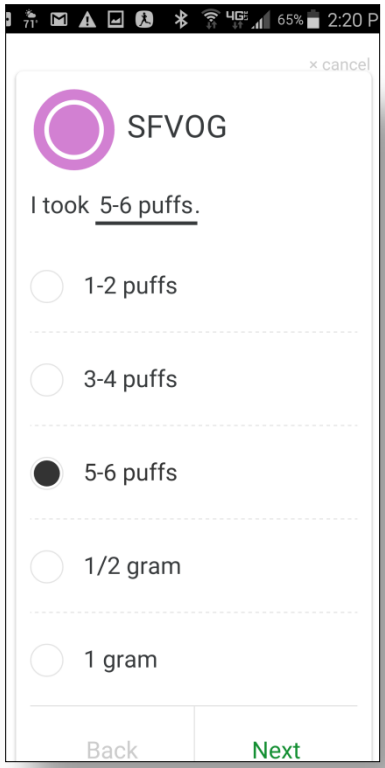

Cannabis Chemotype & Dosage Entry Screens

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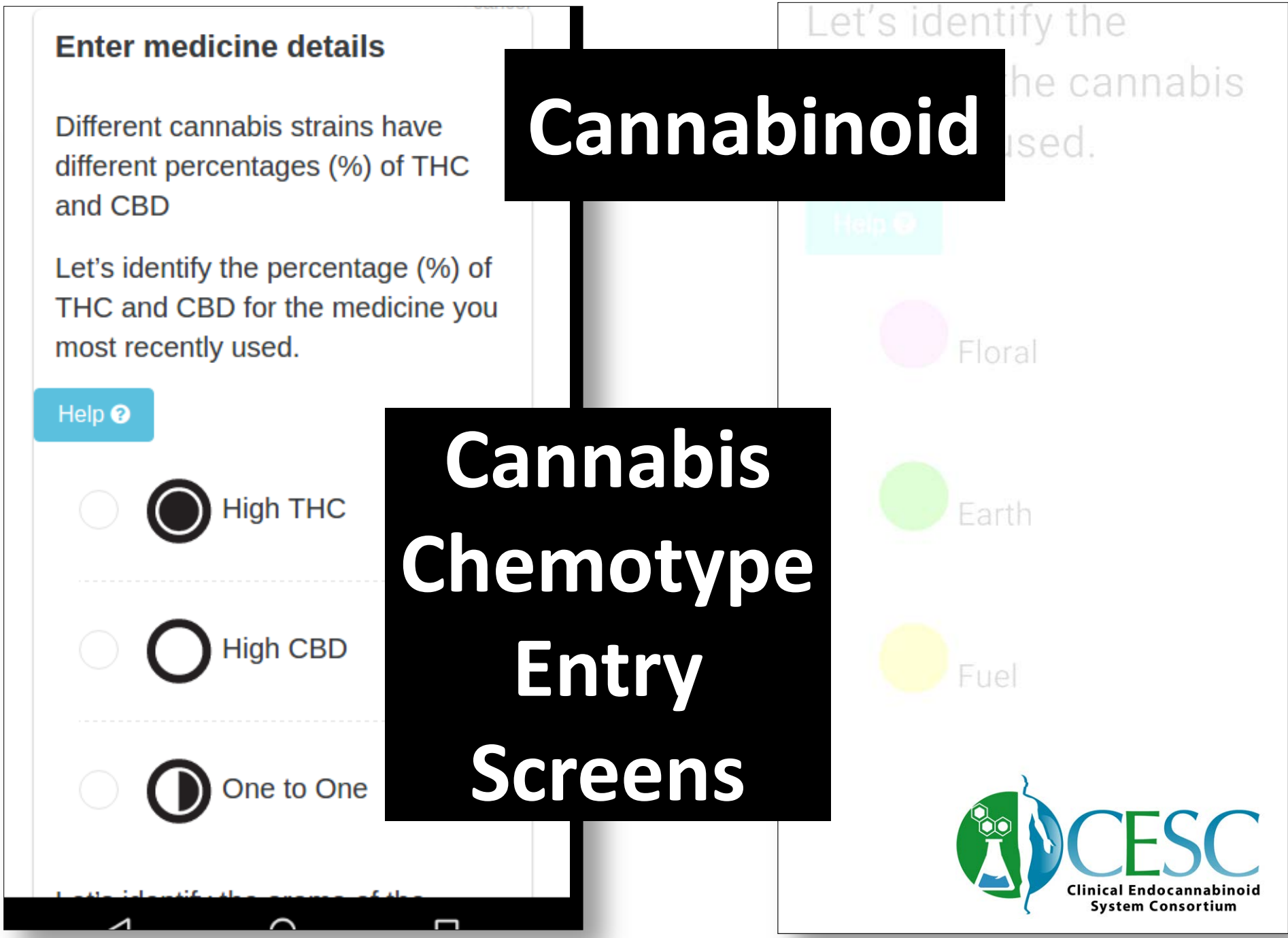
Enter medicine details
Different cannabis strains have different percentages (%) of THC and CBD
Let's identify the percentage (%) of THC and CBD for the medicine you most recently used.
Help
High THC
High CBD
One to One
Let's identify the
he cannabis
used.
Help
Floral
Earth
Fuel
Cannabinoid
Cannabis Chemotype Entry Screens
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Natural Product Classes in Cannabis

- Cannabinoids
- Terpenoids
- Flavonoids
- Stilbenoids
- Alkaloids
- Lignanamides

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PhytoCannabinoids

- Made up of various building blocks
- Cannabinoid Metabolome believed unique to cannabis
- Biosynthesized by different enzymes compartmentalized within the cannabis plant
- Many biosynthesis and degradation pathway intermediates are bioactive

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PhytoCannabinoid Vocabulary

- **THC & THCA** — Tetrahydrocannabinol (ic Acid)
  - **- Δ-9 & Δ-8 THC** — Δ-9 & Δ-8 tetrahydrocannabinol
  - **- THCV** — Tetrahydrocannabivarin
  - **- 11-Hydroxy THC** — 11-Hydroxy tetrahydrocannabinol
- **CBD & CBDA** — Cannabidiol (ic Acid)
- **CBGA** — Cannabigerolic Acid
- **CBN** — Cannabinol

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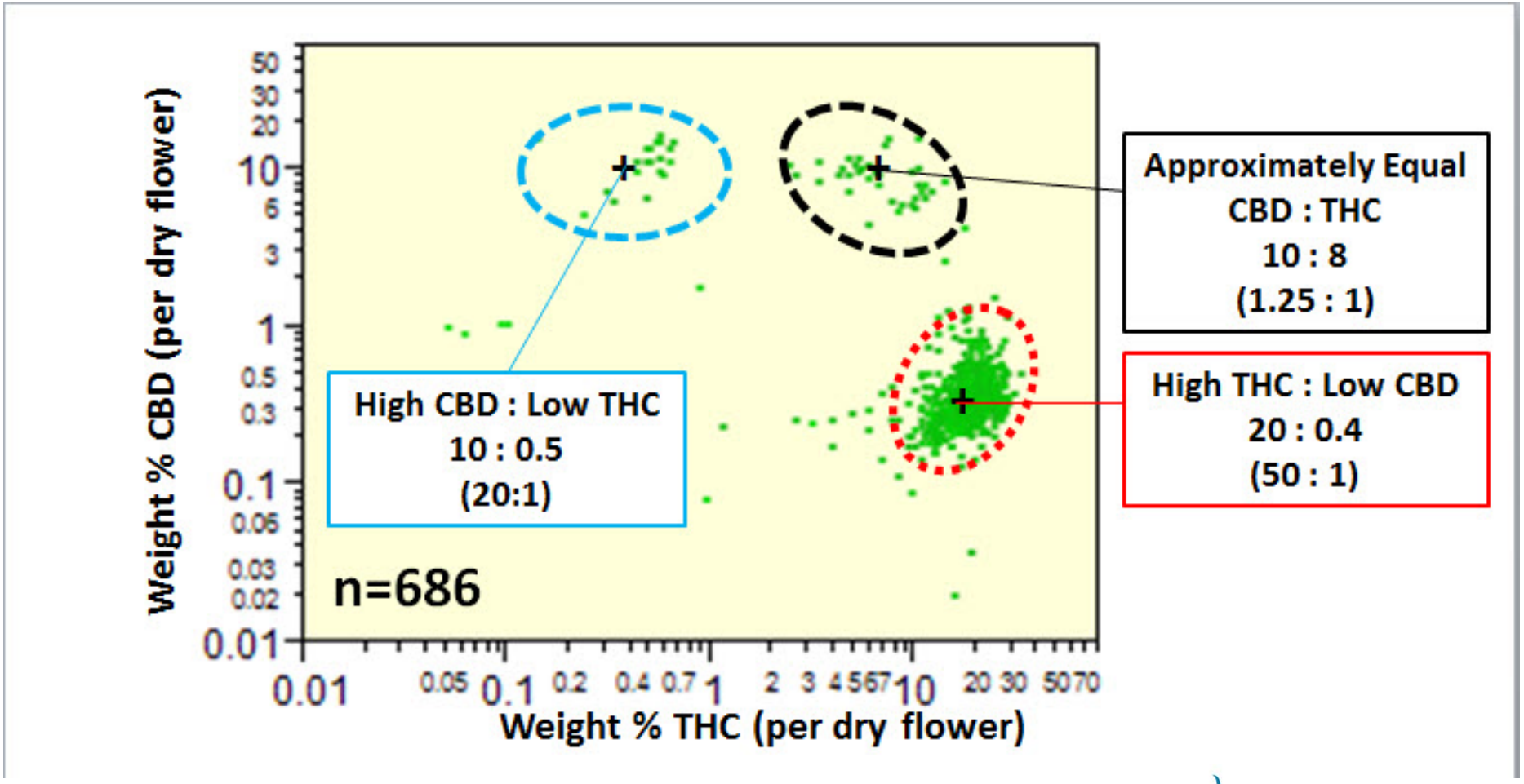
Scatterplot: Cannabis Flower Samples – CBD vs THC



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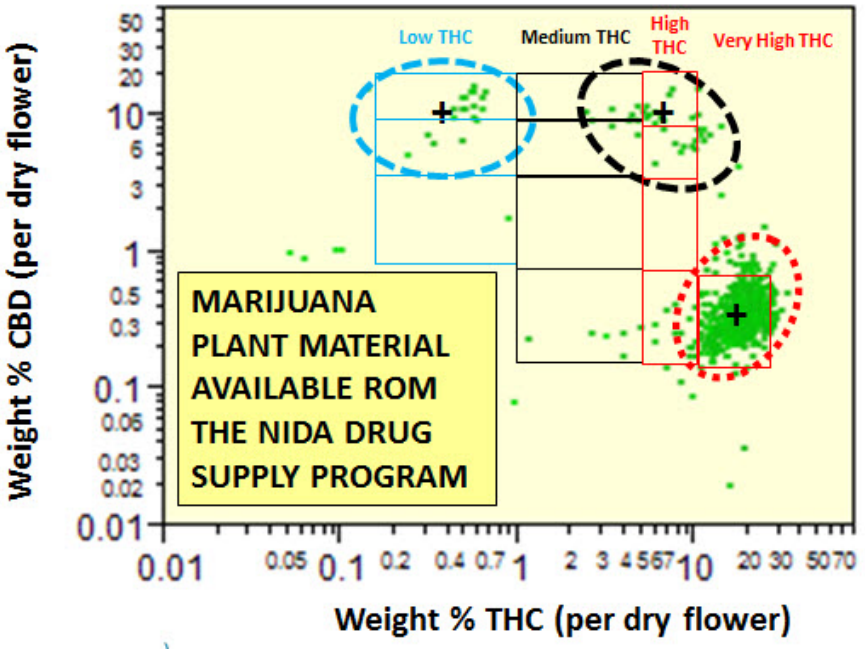
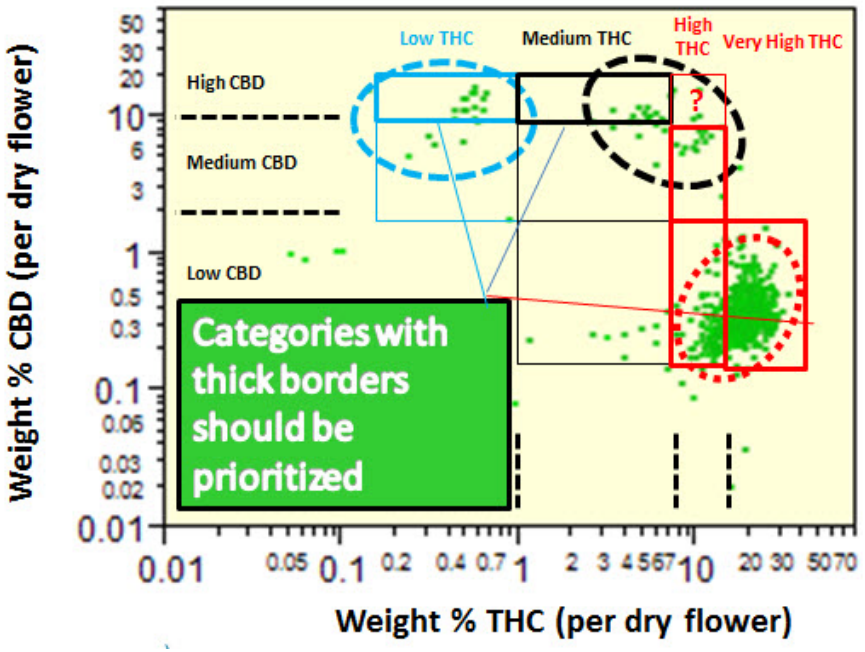
Using the CBD by THC Scatterplot to Define Product Categories



NIDA Bulk Marijuana Categories



CESC Recommended Ranges

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Recommended Ranges for NIDA Bulk Marijuana Categories

Shaded categories should be prioritized

CBD	THC < 1 %	THC Between 1 - 8 %	THC Between 8 – 15 %	THC > 15 %
< 2 %		Medium THC; Low CBD	High THC; Low CBD	Very High THC; Low CBD
Between 2 – 10 %	Low THC; Medium CBD	Medium THC; Medium CBD	High THC; Medium CBD	
> 10 %	Low THC; High CBD	Medium THC; High CBD	High THC; High CBD (may not exist)	

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Cannabinoids: Summary & Conclusions

- 3 major cannabinoid chemotype classes based on CBD : THC Ratio (High , Equivalent, & Low) are evident
- There are “No Go Zones” where certain ratios are not produced naturally by the cannabis plant
- **This scheme establishes a basis for our initial clinical studies programs through The CESC’s Dosing Project**

NOW – WHAT ABOUT TERPENOIDS?

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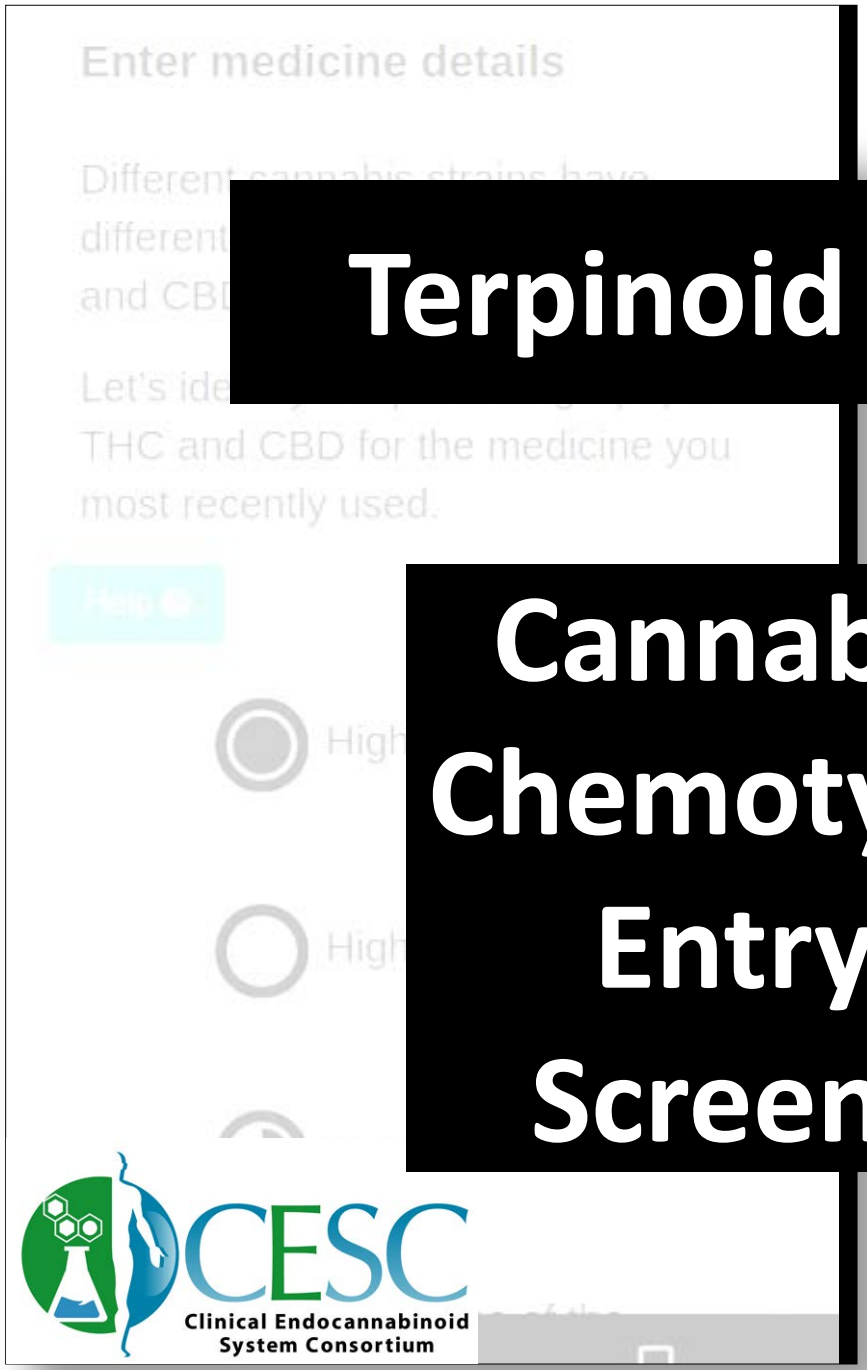
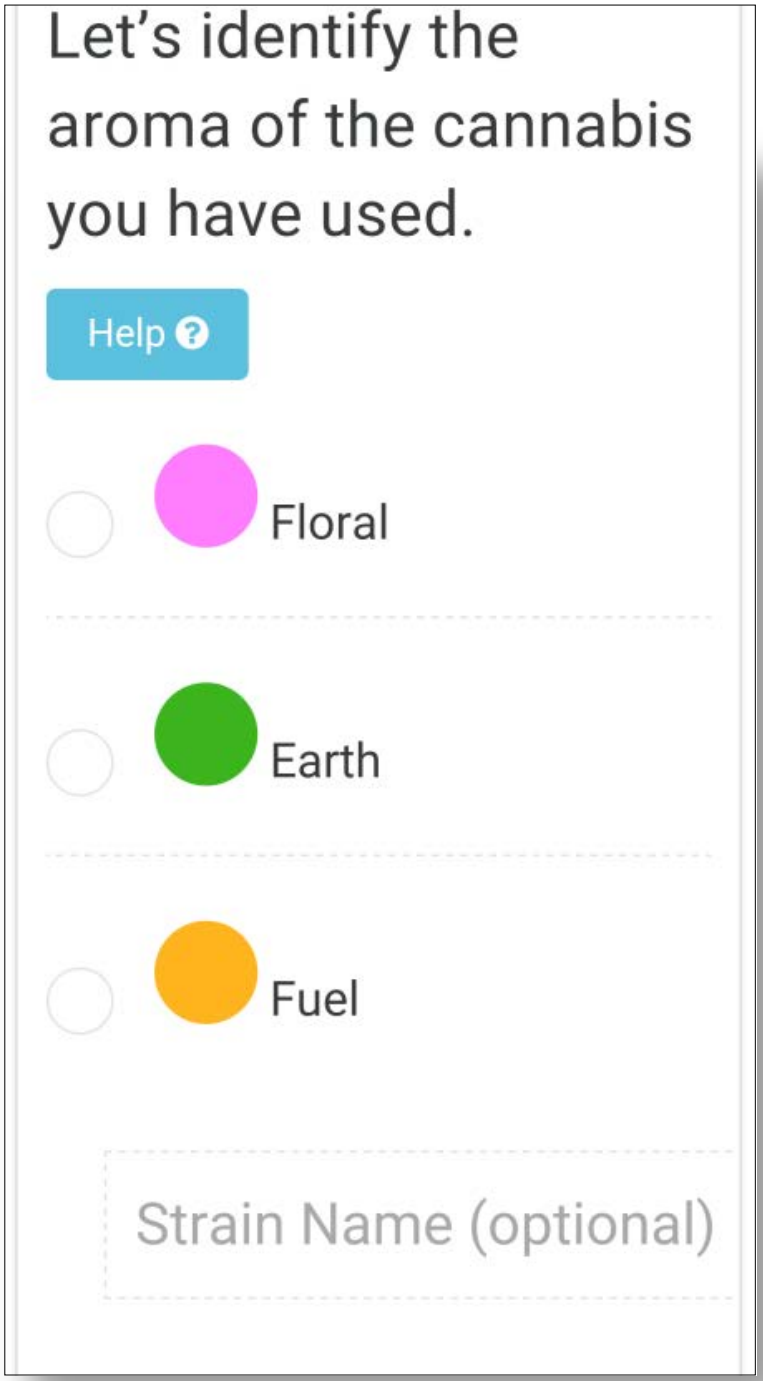
Terpinoid

Cannabis Chemotype Entry Screens





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Terpenoids

- Made up of similar building blocks joined together in different ways
- Terpenoid Metabolome ubiquitous in land plants
- Different biosynthetic enzymes compartmentalized within the cannabis plant
- Promiscuous biosynthetic enzymes make different products from same precursor

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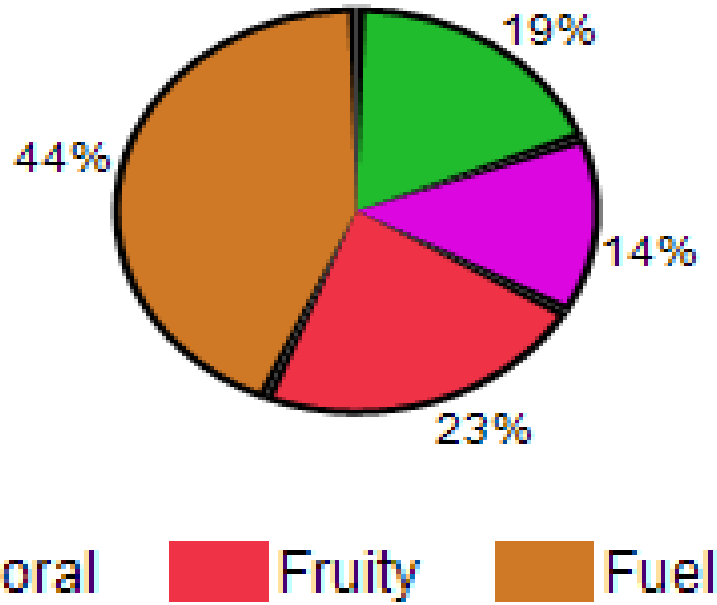
The 2015 Golden Tarp Awards:
Matching Terpenoid Profiles with Aroma Categories

- Humboldt's Light Dep Competition at 2nd Golden Tarp Award (GTA) — Sept. 12, 2015
- All entries are tested for cannabinoids and terpenoids
- 4 aroma categories were judged:



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The 2015 Golden Tarp Awards: Matching Terpenoid Profiles with Aroma Categories (cont'd)

- Contestants decide which aroma category they submit

- The analytical results are now public domain and can be accessed here: http://www.theganjier.com/2015/10/09/winner-and-top-16-results-for-the-2nd-annual-golden-tarp-award

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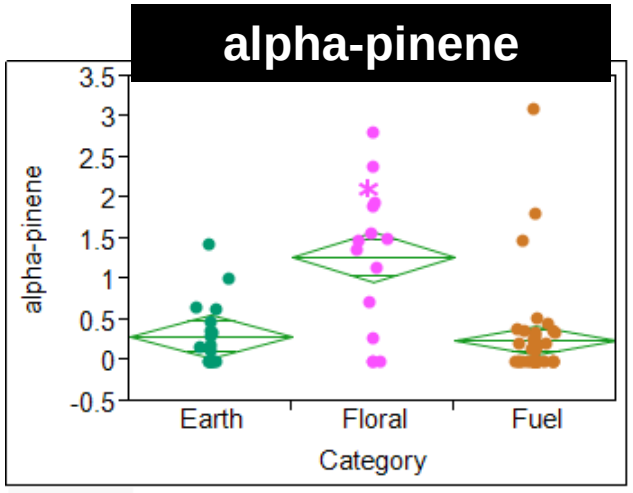
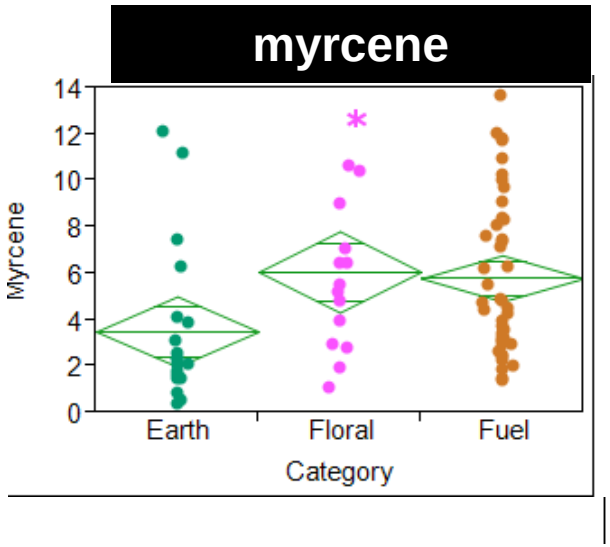
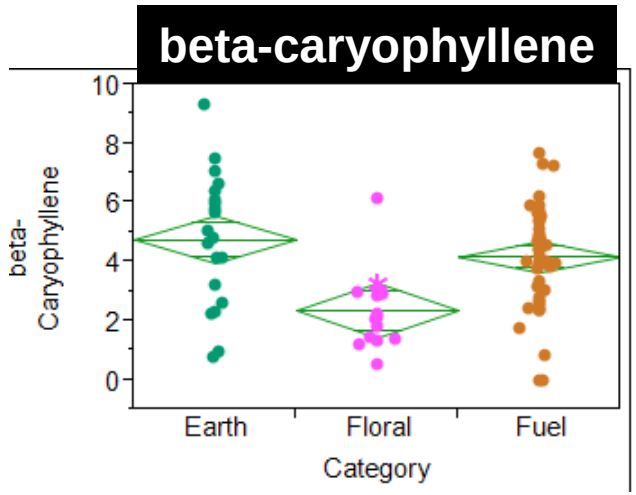
The Terpenoid “Grammar” of the Earth, Floral & Fuel Aroma Categories



Prob > F < 0001*



Prob > F 0.0299*



Prob > F 0.0006*

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The Terpenoid "Grammar" of the Earth, Floral, & Fuel Aroma Categories

Aroma Category	alpha-pinene	myrcene	Beta-caryophyllene
Earth	Low	Low	High
Floral	High	High	Low
Fuel	Low	High	High

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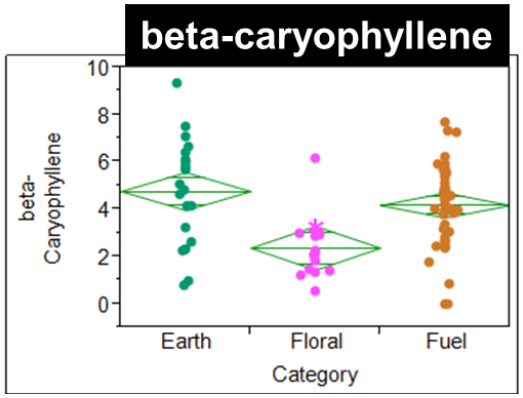

A.-L. Klauke[a,1], I.Racz[a,n,1], B.Pradier[a], A.Markert[a], A.M. Zimmer[a], J.Gertsch[b], A.Zimmer[a]

European Neuropsychopharmacology (2014) 24, 608–620

The Cannabinoid CB2 Receptor-Selective Phytocannabinoid Beta-Caryophyllene Exerts Analgesic Effects in Mouse Models of Inflammatory and Neuropathic Pain

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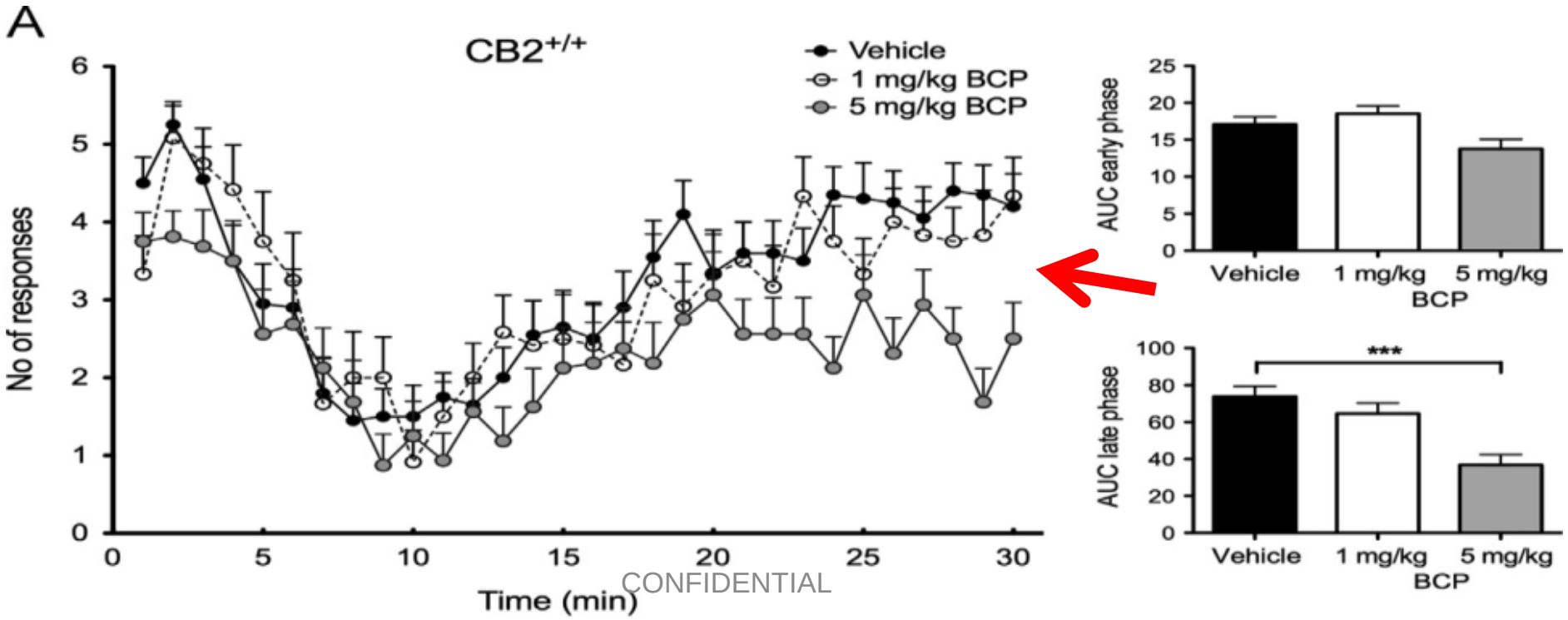

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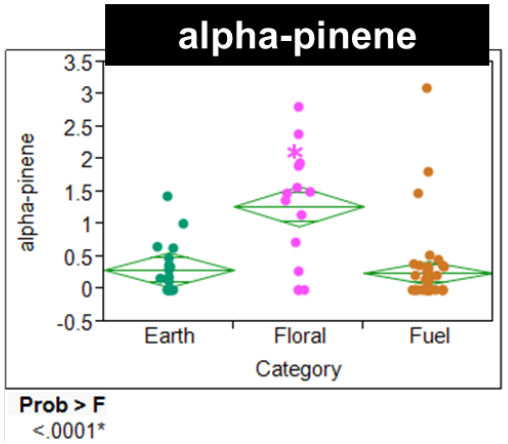

MITSUO MIYAZAWA* AND CHIKAKO YAMAFUJI
Inhibition of Acetylcholinesterase Activity by Bicyclic Monoterpenoids
J.Agric.FoodChem., Vol. 53, No. 5, 2005 1767

Inhibition of Acetylcholinesterase Activity by Alpha-Pinene

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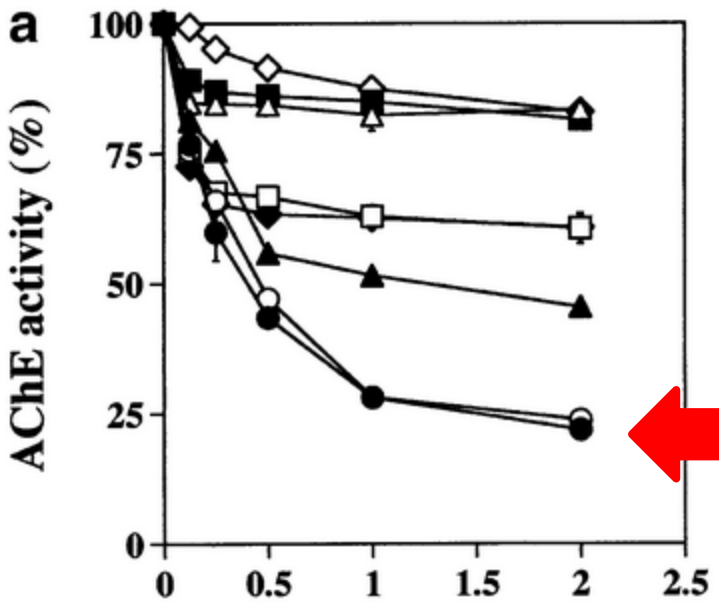
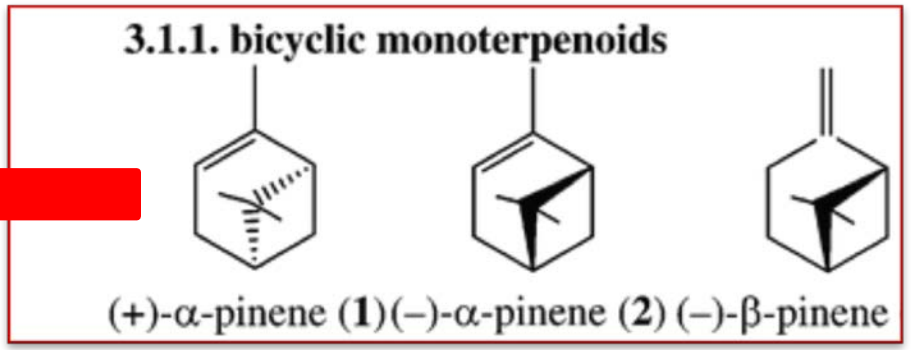
Effect of 3.1.1 bicyclic monoterpenoids (pinane skeleton) on AChE activity



The percentage enzyme activity values for the inhibitors were calculated as compared to the control activity, assumed to be 100%:



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Terpenoids: Summary & Conclusions

- 3 major terpenoid chemotype classes based on aroma category have been defined: earth, floral & fuel

- We recommend that the beta-caryophyllene : alpha-humulene ratio (3:1) be used as an analysis QA parameter and also serves as an identity parameter for cannabis

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Terpenoids: Summary & Conclusions (cont'd)

- Terpenoid content stability during cannabis product processing needs to be investigated and controlled

- **<u>This scheme establishes a basis for our initial clinical studies programs through The CESC's Dosing Project</u>**

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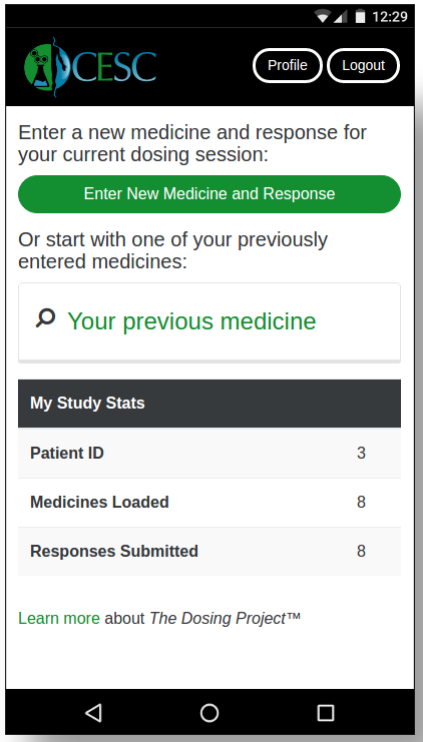

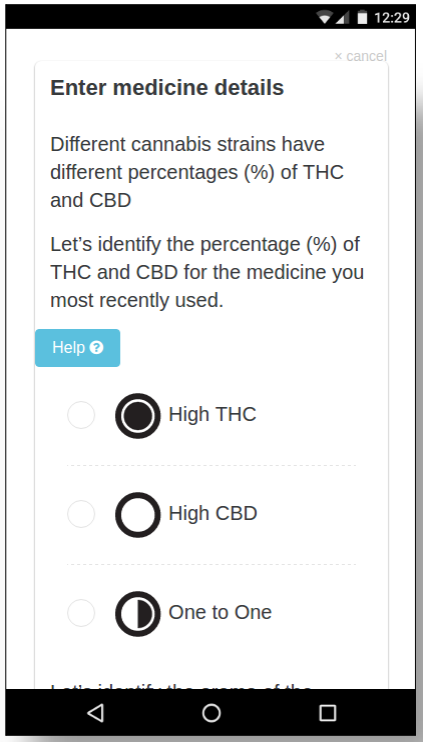

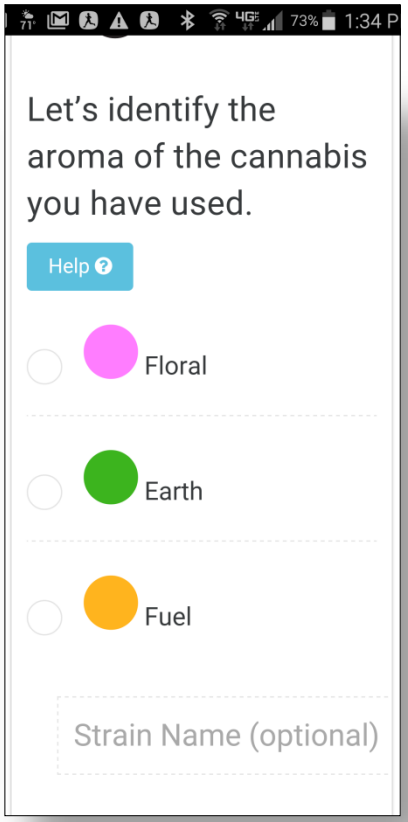

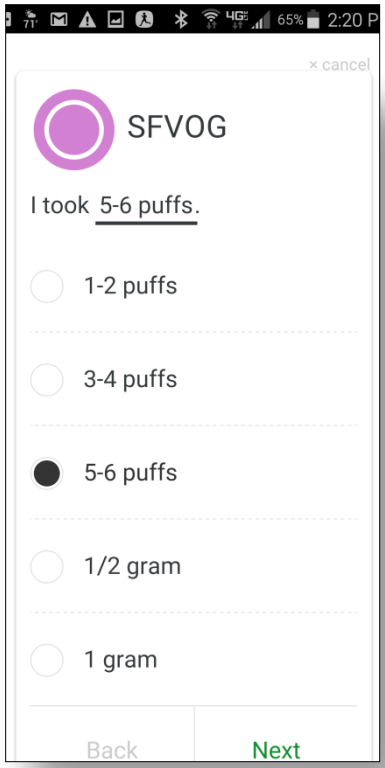

Cannabis Chemotype & Dosage Entry Screens

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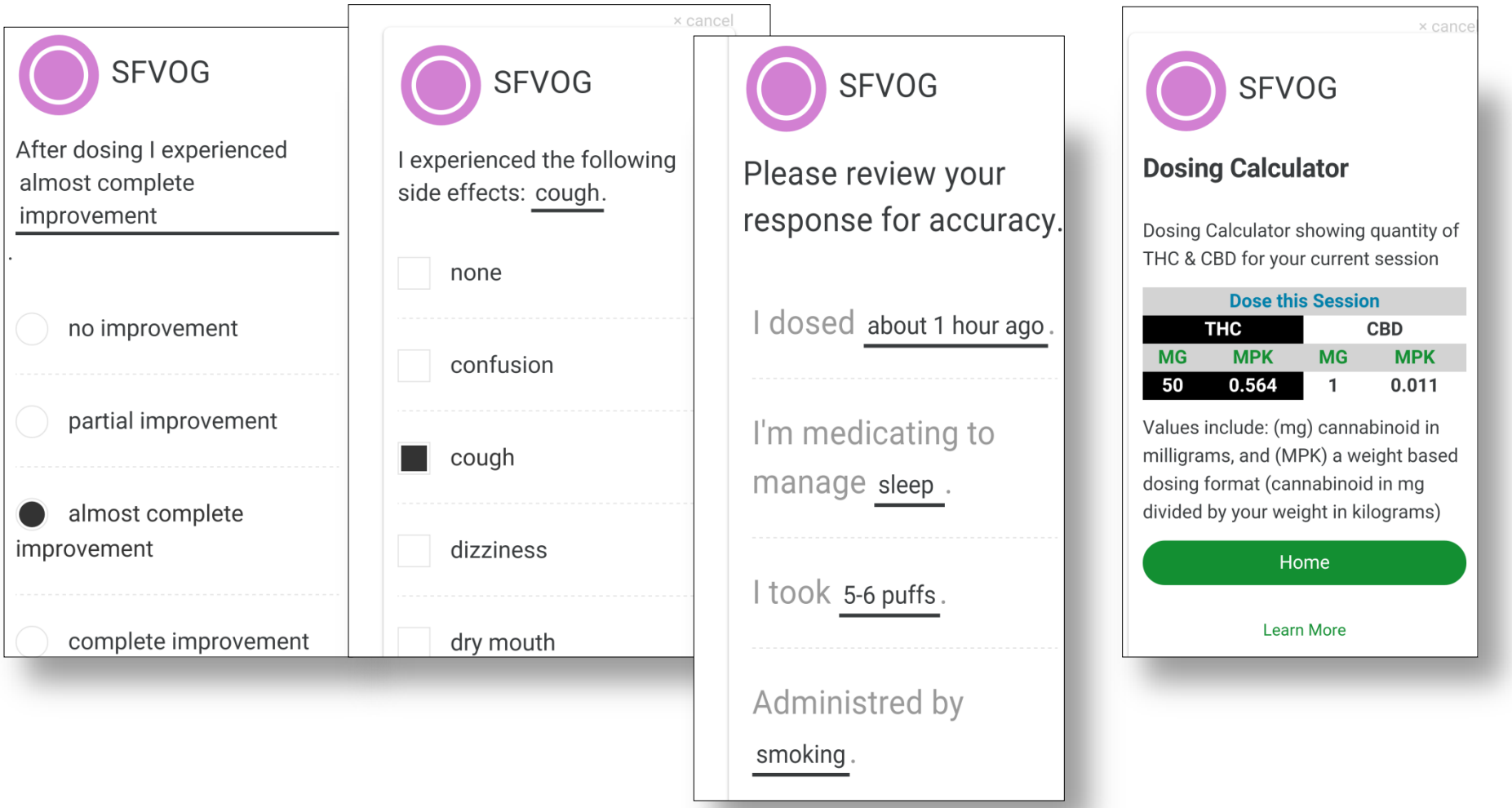

Response Screens

Dosing Calculator

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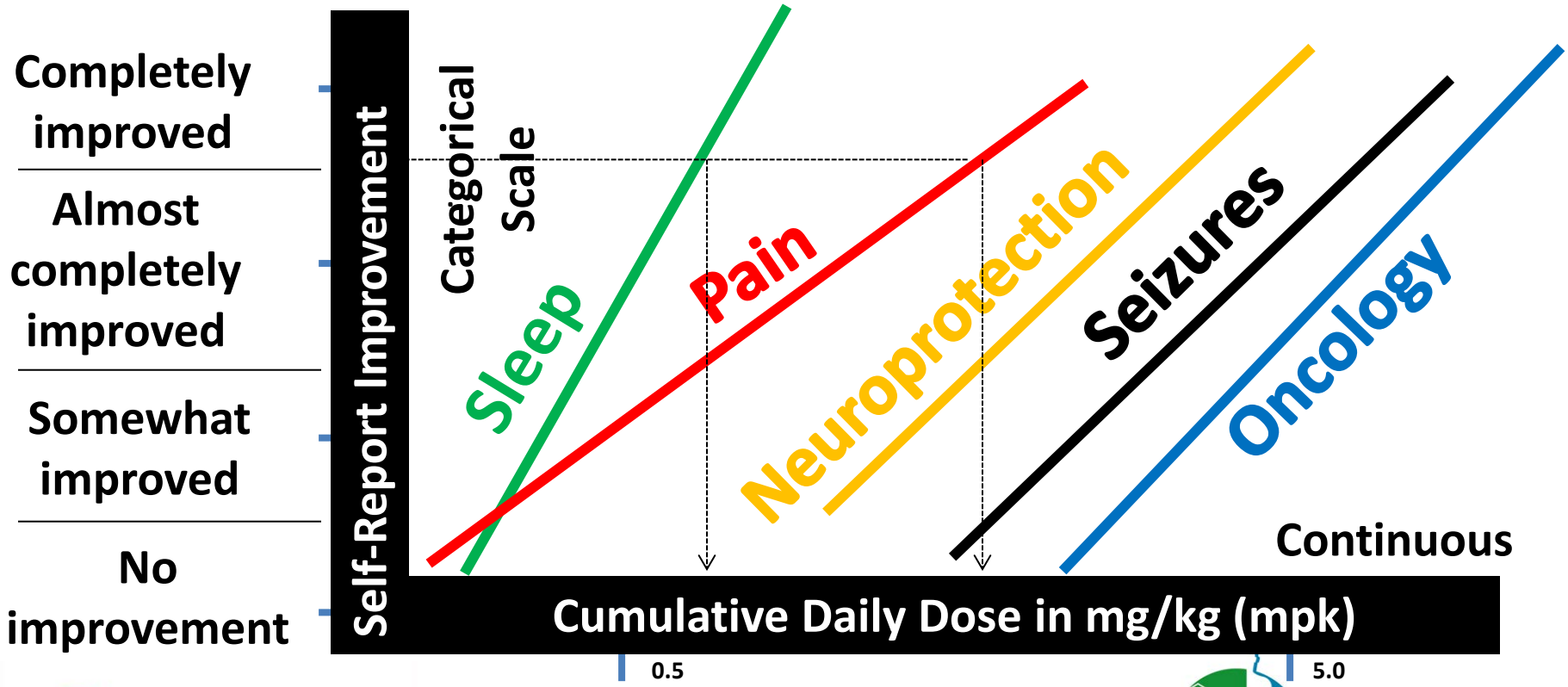
The Dosing Project:

Logistic Regression with Effect Likelihood Ratio Tests and Inverse Prediction to Determine Optimal Dosing



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The Dosing Project:
Overview of Proof of Concept (POC) Phases

Determine Weight-based Dosing Efficacy of Major Cannabis Flower Chemotype Groups For Symptom Relief of Pain & Disordered Sleep

I. Phase 1.0 – Initial Roll-Out
II. Phase 1.1 – Implement ICD10 Code Dx
III. Phase 1.2.1 – Incorporate Lab-Derived Chemotype Data (Cannabinoid)
IV. Phase 1.2.2 – Incorporate Lab-Derived Chemotype Data (Terpenoid)
V. Phase 1.2.3 – Incorporate Point-of-Use Device Chemometric Data (Cannabinoid + Terpenoid)
VI. Phase 1.3 – Expand Modes of Administration (MOAs) to Oils/Concentrates, Edibles, & Topicals

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The Dosing Project Can Help Your Product Development Effort to:

- ✓ **Determine Dose for Optimal Efficacy of Your Product**
- ✓ **Compare Your Product with Others in Its Category**
- ✓ **Track & Quantify Side Effect Signals for Your Product**

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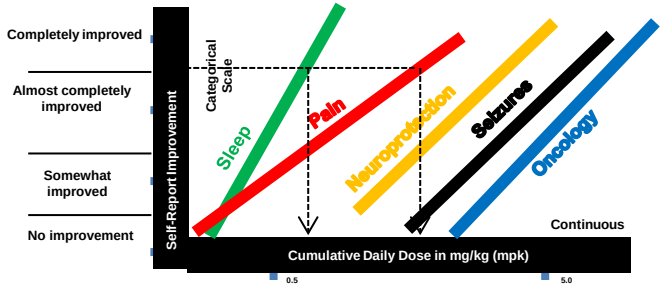
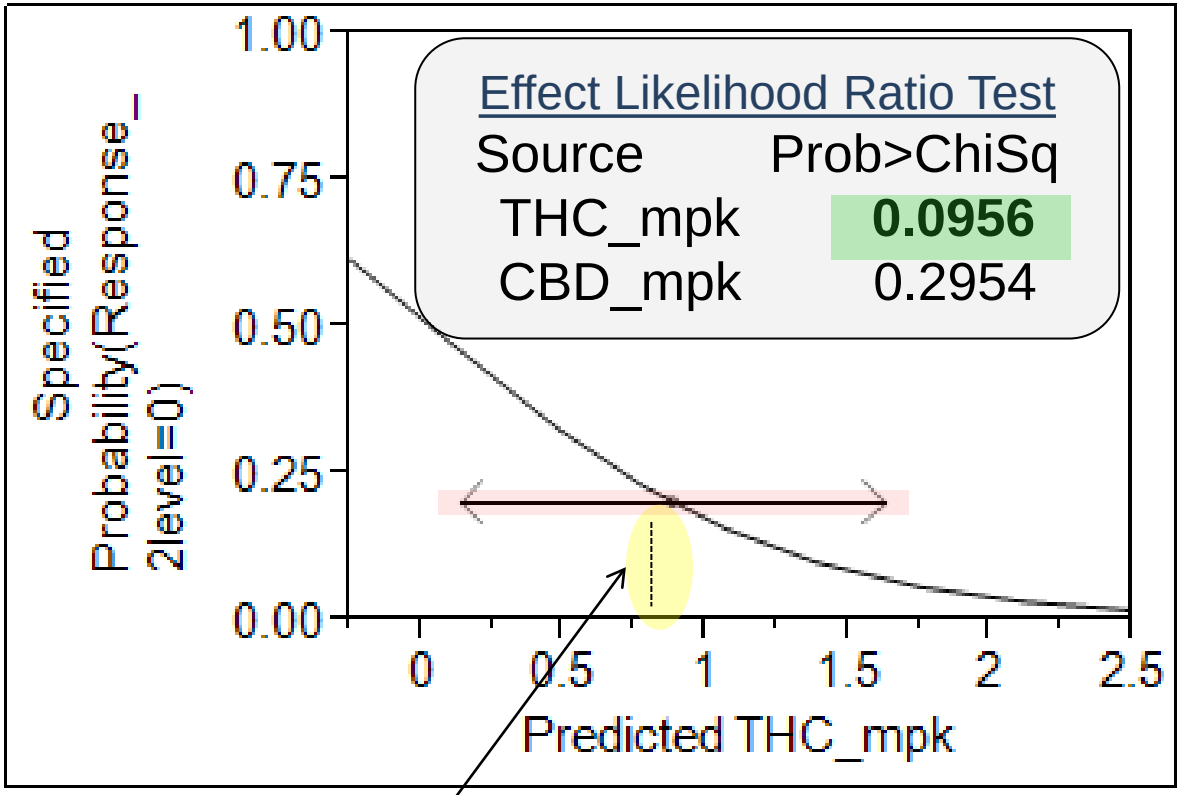
Determine Dose for Optimal Efficacy of Your Product





Pain

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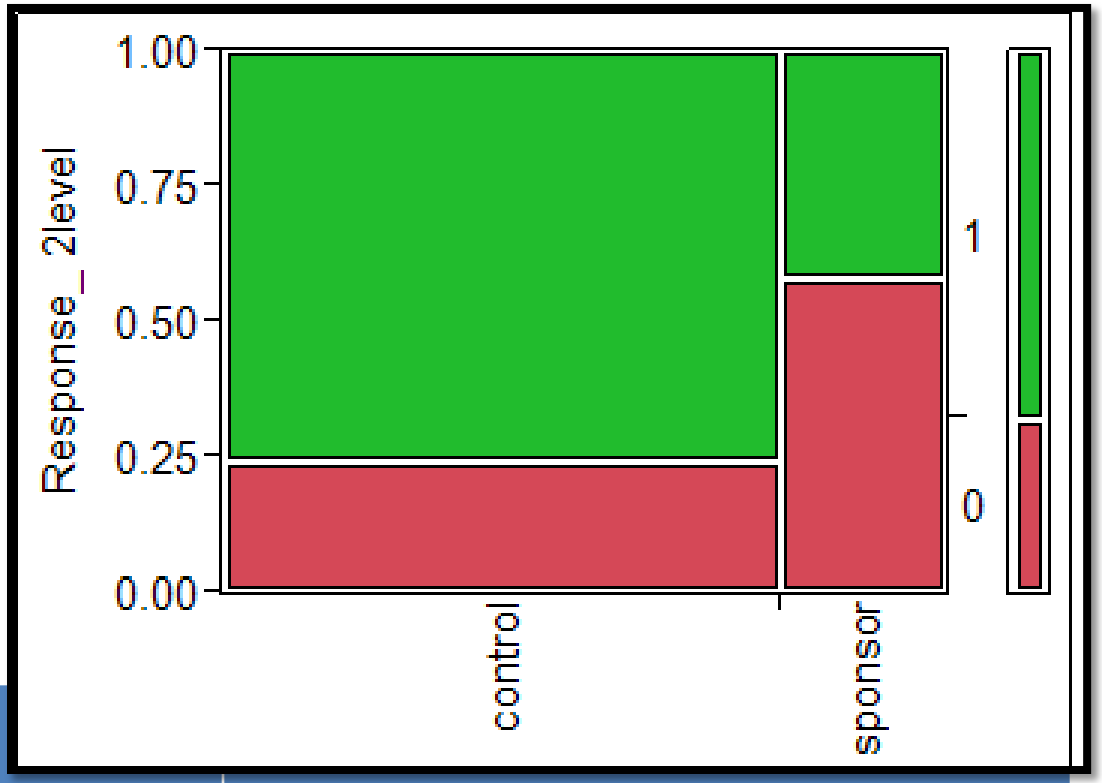
Inverse Prediction

Specified Probability	Predicted THC_mpk	Lower 95%	Upper 95%
80%	**0.88**	0.14	1.63

Compare Your Product with Others in Its Category



Fisher's Exact Test	Probability	That Efficacy Is (not):
Left	0.0335	greater for control
Right	0.9939	greater for sponsor
2-Tail	0.0382	different across agents

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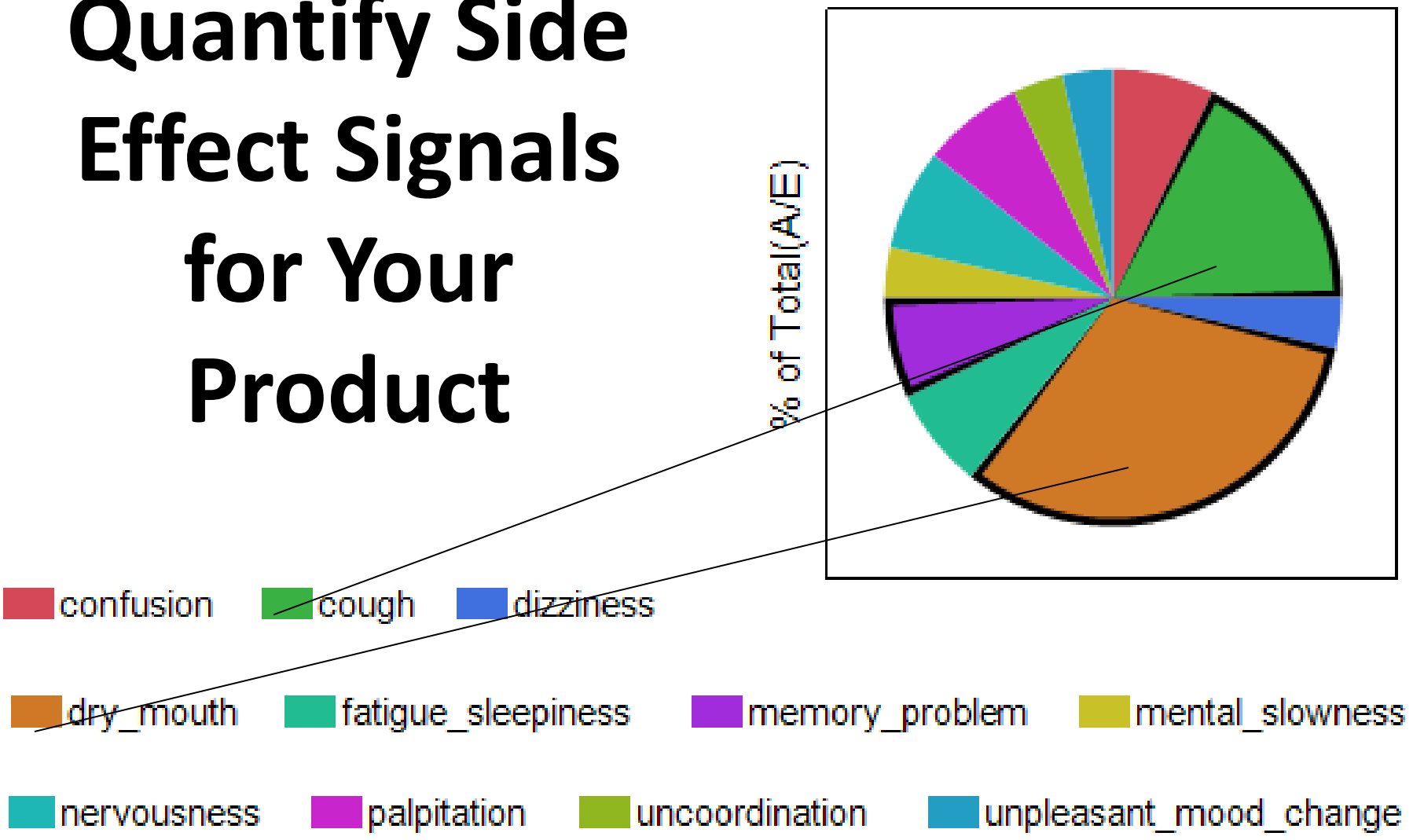
Track & Quantify Side Effect Signals for Your Product



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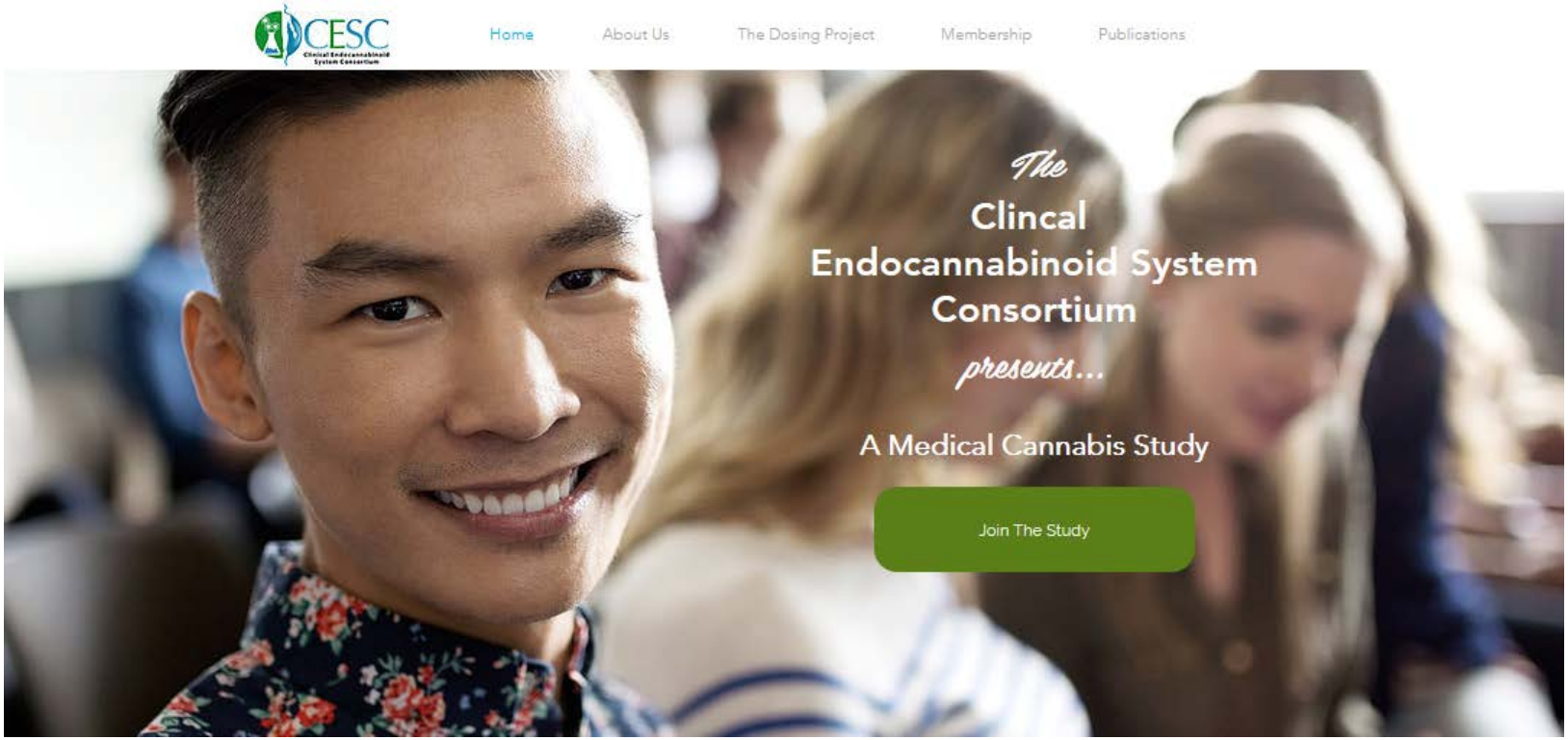
The Dosing Project: Join The Study



http://www.thecesc.org/

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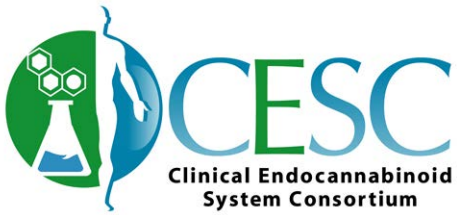
SUPPLEMENTAL SLIDES



Building Blocks for Key Cannabis Product Classes

TYPE		BUILDING BLOCK I	BUILDING BLOCK II	BUILDING BLOCK III
CANNABINOID - C H O				
THC-like	**5C side chain**	**N-hexanoyl CoA**	3X malonyl-CoA	GDP
THCV-like	**3C side chain**	**N-butyl CoA**	3X malonyl-CoA	GDP
FLAVONOID – C H O N				
		p-coumaroyl-CoA	3X malonyl-CoA	GDP

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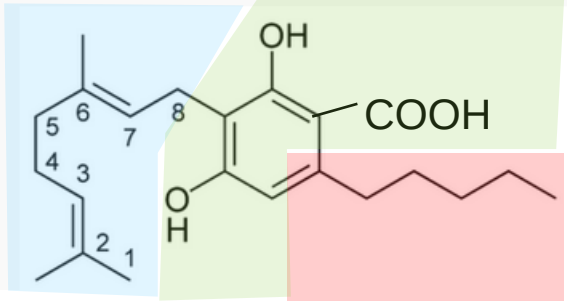
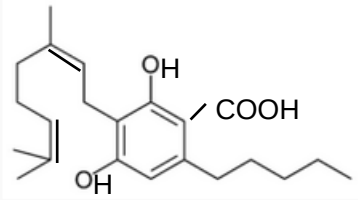
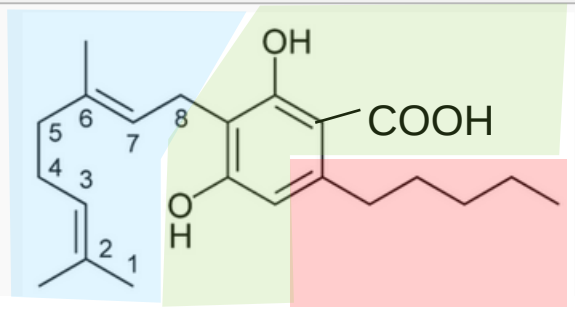
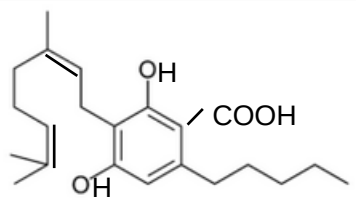
Cannabigerol-type **CBG**		

BUILDING BLOCK i

Cannabigerol-type **CBG**		

Building Blocks for CBGA – The THCA & CBDA Precursor

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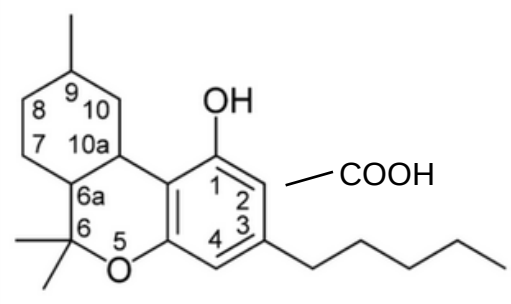
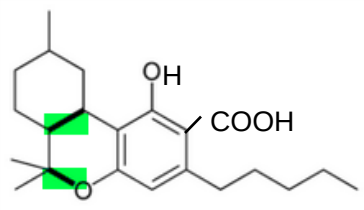
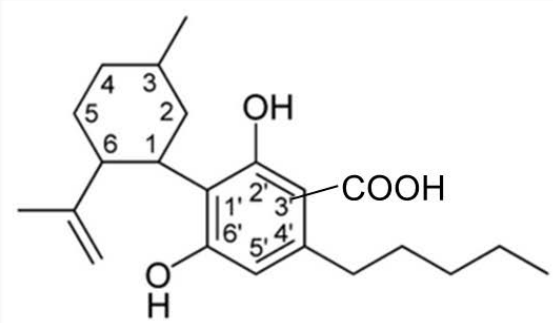
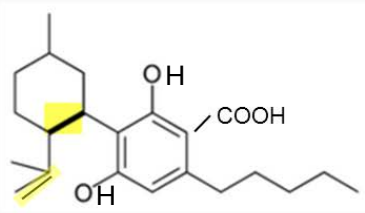
Tetrahydrocannabinol- and Cannabinol-type **THC, CBN**		
Cannabidiol-type **CBD**		

Biotransformation of CBGA to THCA & CBDA

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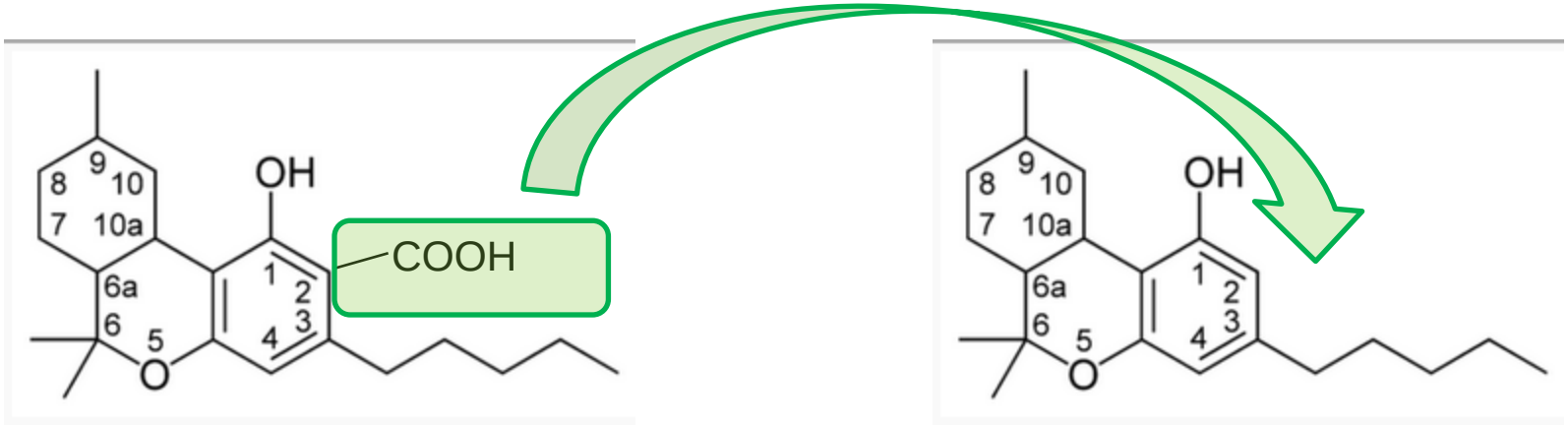

Δ 9 Tetrahydrocannabinolic Acid

Δ 9 Tetrahydrocannabinol

THCA Decarboxylation to THC by Heat or Light

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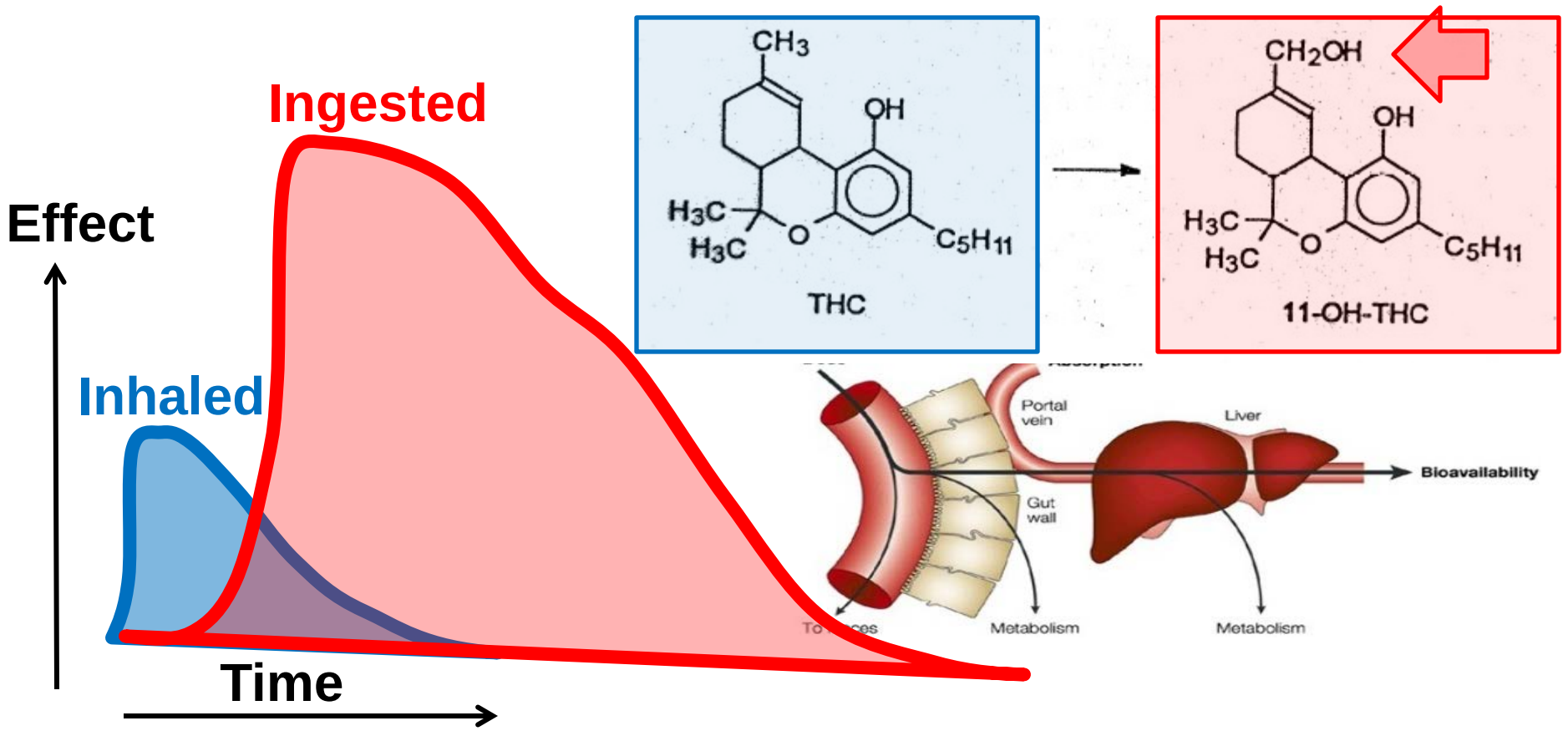

In Vivo Biotransformation of THC to 11-OH-THC

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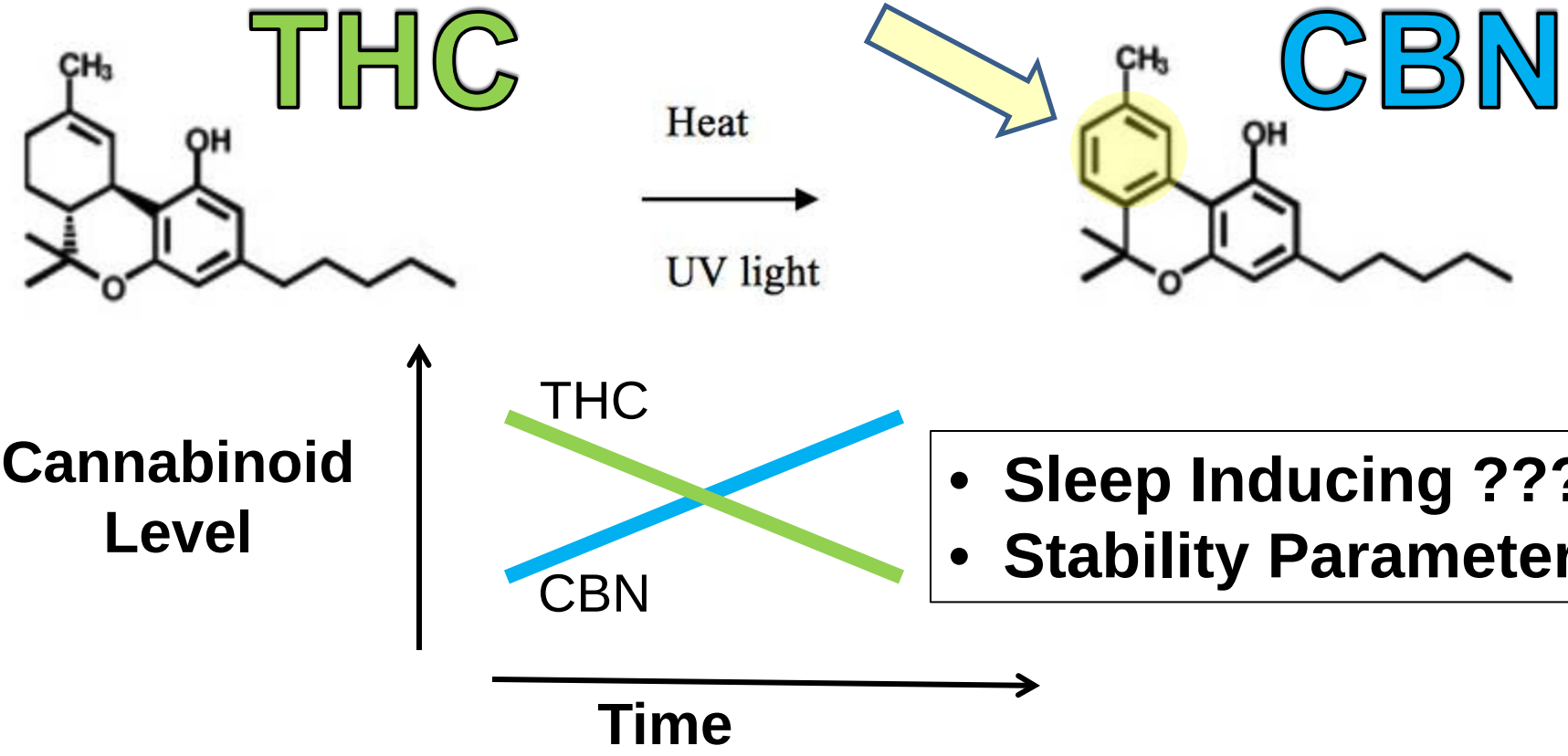

Oxidation of THC Creates CBN

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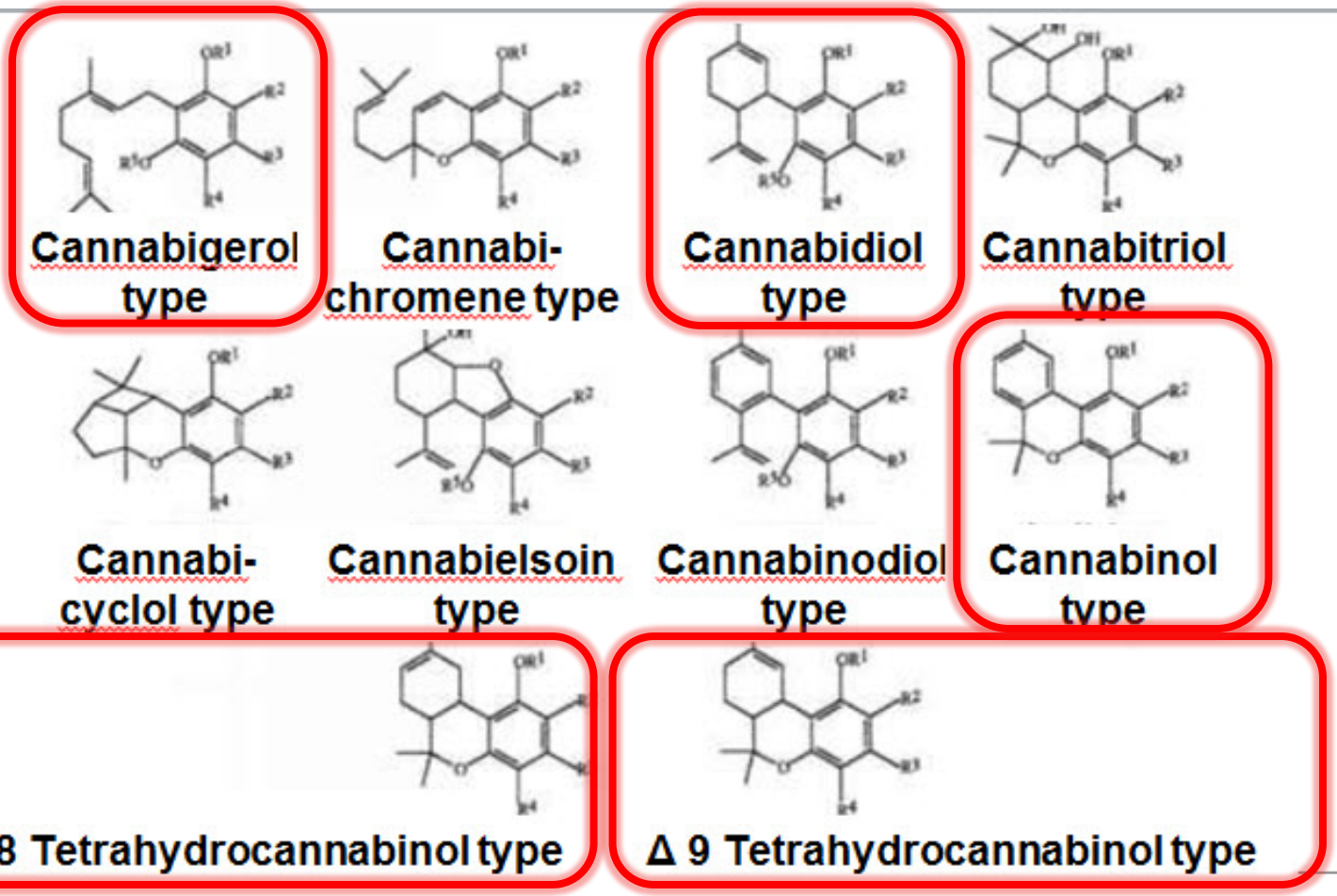
Cannabinoid Structural Types



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Building Blocks for Key Cannabis Product Classes

TYPE	BUILDING BLOCK I	BUILDING BLOCK II	BUILDING BLOCK III
TERPENOID - C H O			
Monoterpenoid (C10)			GDP
Sesquiterpenoid (C15)			FDP / NDP

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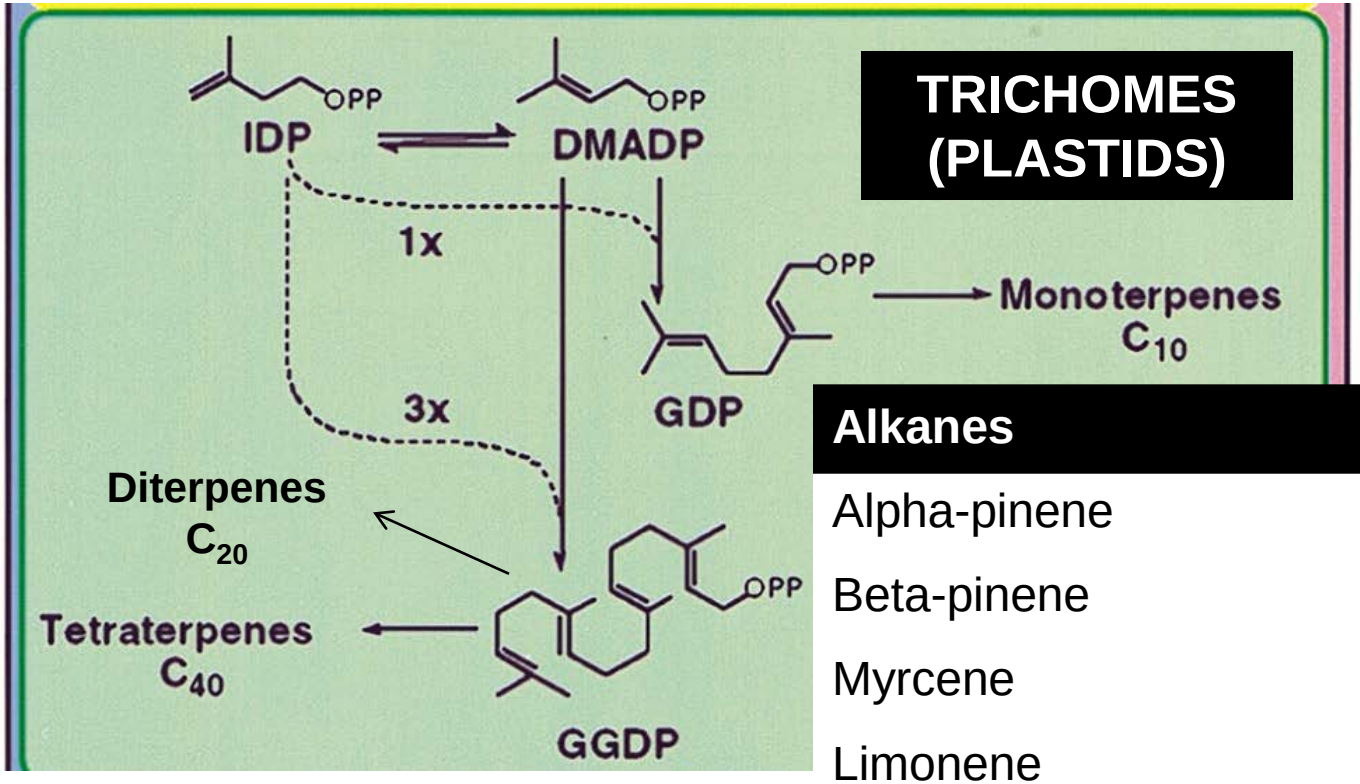
Organization of MonoTerpenoid Biosynthesis in Plants



Alkanes	Alcohols
Alpha-pinene	Linalool
Beta-pinene	Fenchol
Myrcene	Menthol*
Limonene	Borneol
Ocimene	**Alpha-terpineol**
	Geraniol

Plant terpenoid synthases: Molecular biology and phylogenetic analysis

Proc. Natl. Acad. Sci. USA vol. 95, pp. 4126–4133, April 1998

JORG BOHLMANN*†, GILBERT MEYER-GAUEN‡, AND RODNEY CROTEAU*§

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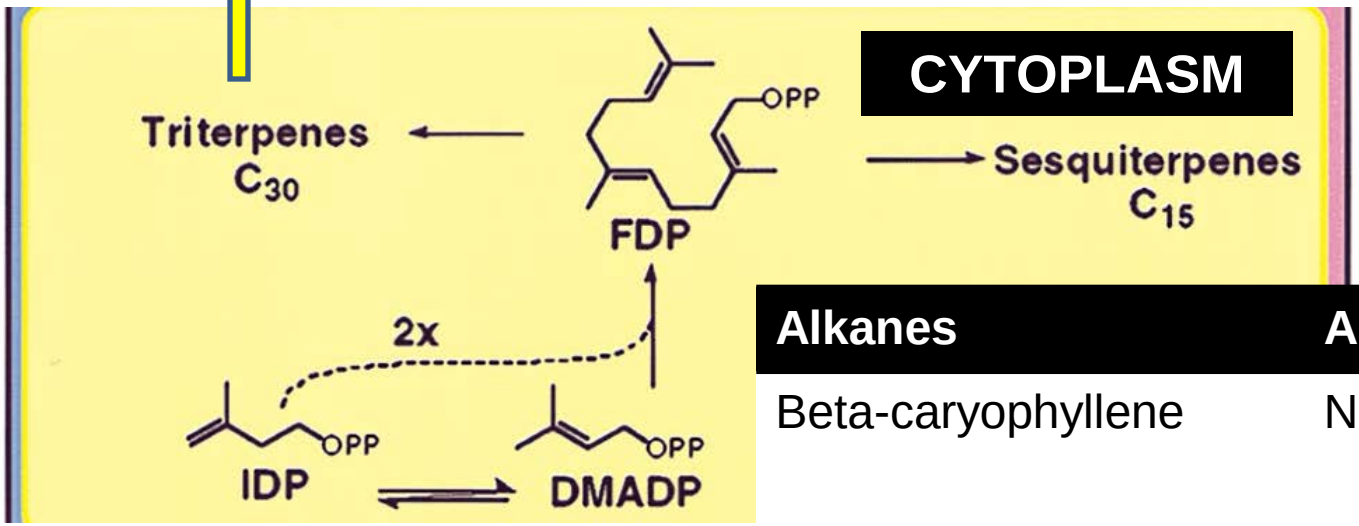
Organization of SesquiTerpenoid Biosynthesis in Plants

Cuticular Wax



Alkanes	Alcohols
Beta-caryophyllene	Nerolidol
Alpha-humulene	Guialol
Valencene	Alpha-bisabolol
Farnesene	

Plant terpenoid synthases: Molecular biology and phylogenetic analysis
Proc. Natl. Acad. Sci. USA vol. 95, pp. 4126–4133, April 1998
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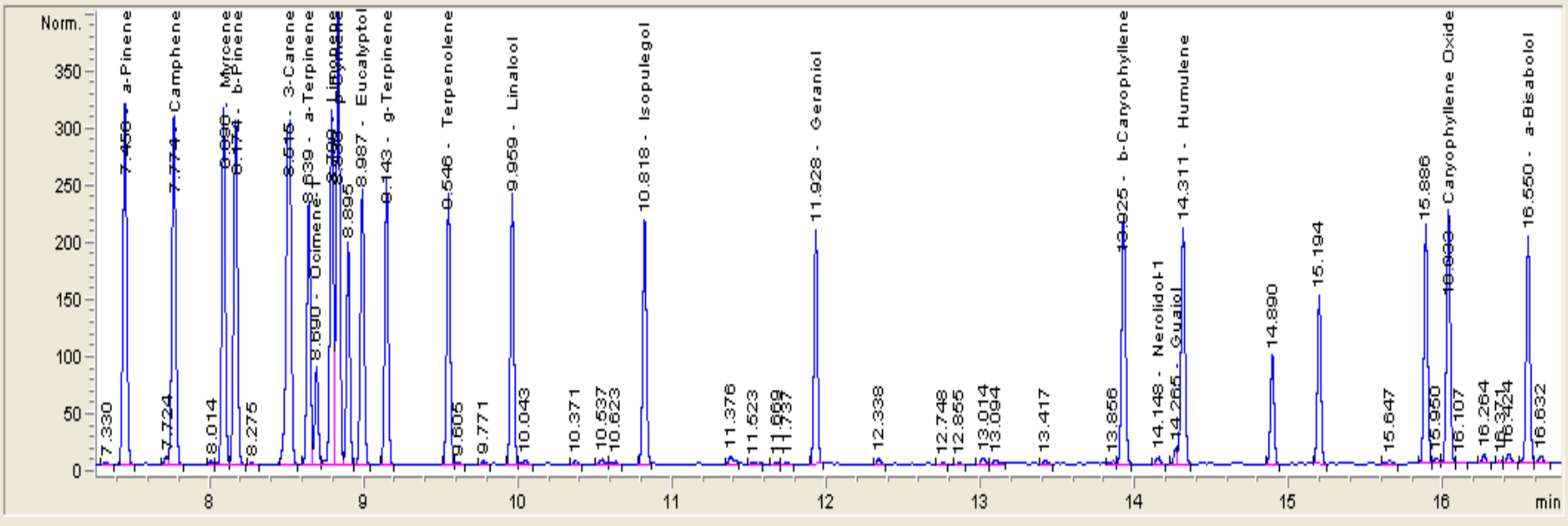
Complexity of Chromatograms



Co-elution of terpenoids and/or mis-identification of analyte peaks can produce inaccurate results

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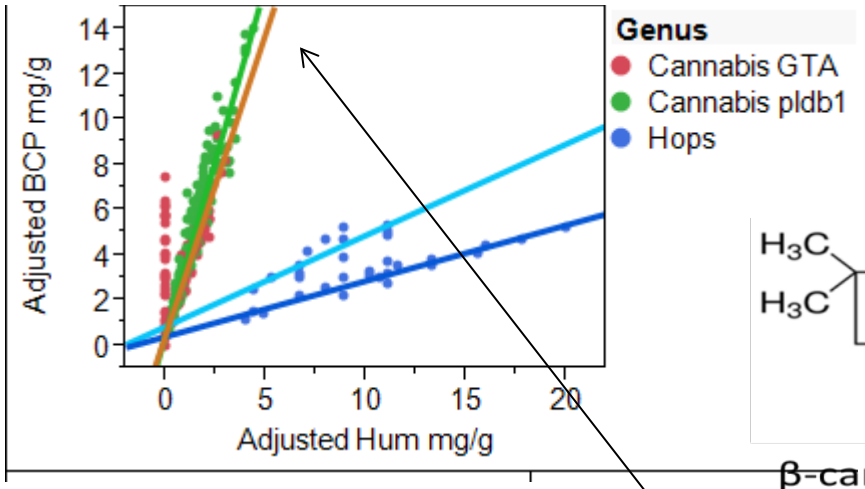
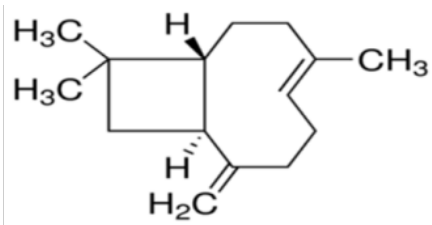
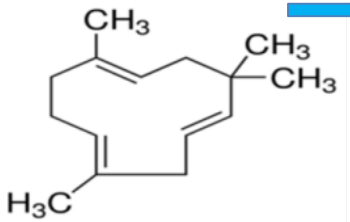
Ratio of Beta-Caryophyllene : Alpha-Humulene in Cannabis & Hops





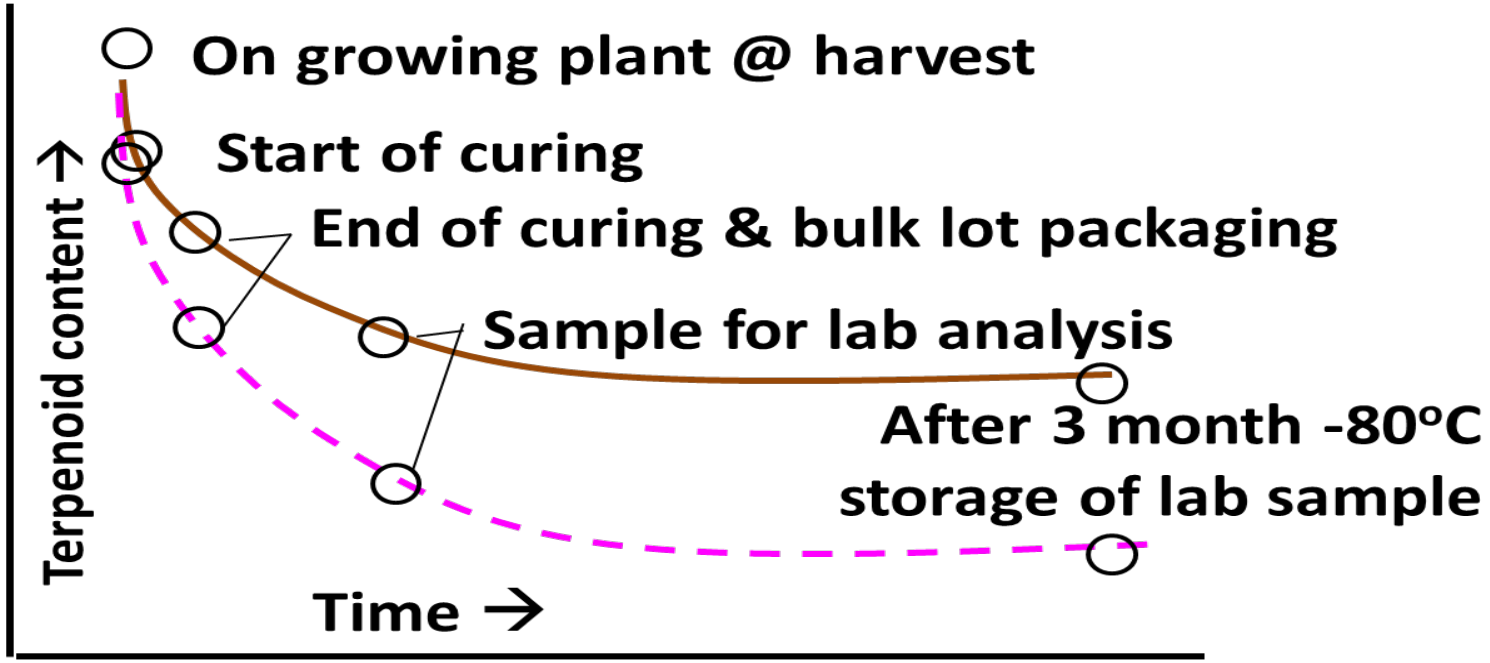
β-caryophyllene



α-humulene

Group	N	Intercept	Ratio BCP/ Ahum	Ratio Std Error of Estimate	R^2
A	14	0.88	0.40	± 0.07	0.76
B	20	0.43	0.25	± 0.01	0.94
Db1	201	0.60	3.09	± 0.06	0.92
GTA	69	0.57	2.67	± 0.13	0.87

Hypothetical Loss of MonoTerpenoid & SesquiTerpenoid Content with Cannabis Processing Time



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