Advancements in the Chemical Synthesis of Natural Cannabinoids

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NATSYN naturally synthetic

In partnership with, McMaster University

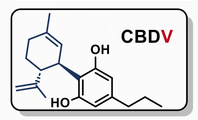
PEREGRINE PRECISION SYSTEMS

The "Up-and-Comers" A look at on-going research and clinical trials involving minor cannabinoids

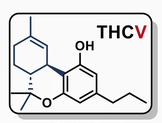
A quick summary of clinical trial findings to the right

The details down below

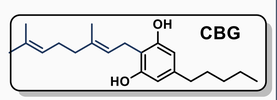
Summarized reported results



Autism Spectrum Disorder - Hyperconnectivity levels reduced to neurotypical levels
Epilepsy - 40% reduction in seizure frequency

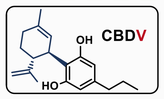


Diabetes - decreased fasting plasma glucose levels



Cosmetics - skin inflammation

**all references are located below in the full details of this literature and patent search*



Clinicaltrials.gov Metrics
- **9 total studies; 1 terminated, 5 recruiting, 2 completed, 1 unknown**
- **No results posted to date**
- **Topics/conditions:** Prader-Willi Syndrome, androgenic alopecia treatment, autism spectrum disorder and ADHD

SciFinder Metrics
- **1189 total references.** **241 journal articles, 941 patents, 24 reviews.** Most publications in 2022 at *297.*
  - **1065 of the references represent some form of biological study; 941 hits of pharmacological activity**
  - **Topics/conditions:** cognitive function, neurodegeneration, cancer, epilepsy, nausea/motion sickness, IBS *and more*

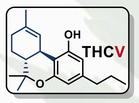
- **4 Clinical Trial reports**

***Ref*:** Pretzsch, C. M. *et al.* **"Modulation of striatal functional connectivity differences in adults with and without autism spectrum disorder in a single-dose randomized trials of CBDV"** *Molecular Autism*, **2021**

Results: Individuals with autism spectrum disorder had their hyperconnectivity levels reduced to neurotypical levels

***Ref*:** Brodie, M.J. *et al.* **"A P2 Randomized Controlled Trial of the Efficacy and Safety of CDBV as Add-on Therapy in Participants with Inadequately Controlled Focal Seizures"**

Results: 40% reduction in seizure frequency



Clinicaltrials.gov Metrics
- **6 total studies; 4 complete, 2 recruiting**
- **1 trial with posted results to date** *(discussed below)*
- **Topics/conditions:** diabetes management, weight-loss, and pharmacokinetics/safety data

Study with Results: "GWP42003 (CBD) – GWP42004 (THCV) Together Plus Alone in Type II Diabetes"
- Sponsored by Jazz Pharmaceuticals
- ***Published as***: *Jadoon, K. A. et al. "***Efficacy and safety of cannabidiol and tetrahydrocannabivarin on glycemic and lipid parameters in patients with type 2 diabetes: A randomized, Double-blind, placebo-controlled parallel group pilot study"** *Diabetes Care* **2016**, *39*, 1777-1786

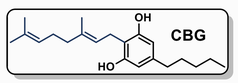
Results: Compared to placebo, THCV *significantly decreased fasting plasma glucose levels* and improved pancreatic B-cell function. THCV could represent new therapeutic agent for glycemic control in subjects with type 2 diabetes.

SciFinder Metrics
- **1130 total references** **303 journal articles, 819 patents, 25 reviews.** Most publications in 2021 at *219.*
  - **Topics/conditions:** THC use detection, obesity, diabetes, nausea, cognitive function, arthritis, IBS

- **8 Clinical Trial reports**

***Ref*:** *Rzepa, E. et al.* "**The CB1 Neutral Antagonist Tetrahydrocannabivarin Reduces Default Mode Network and Increases Executive Control Network Resting State Functional Connectivity in Healthy Volunteers"** *International Journal of Neuropsychopharmacology*, **2016**, *19*

Results: Treatment with CB1 neutral antagonist THCV decreases resting state functional connectivity. This effect profile suggests possible therapeutic activity of THCV for obesity, where functional connectivity has been found to be altered in these regions.



Clinicaltrials.gov Metrics
- **9 total studies; 1 complete, 8 recruiting**
- **No results posted to date**
- **Topics/conditions:** sleep, chronic headache/migraine, pain, appetite loss, ADHD, nausea

SciFinder Metrics
- **1770 total references** **578 journal articles, 1177 patents, 37 reviews.** Most publications in 2021 at *105.*
- **7 Clinical Trial reports**

***Ref*:** *Brierley, D. I. et al.* "**Chemotherapy-induced cachexia dysregulates hypothalamic and systemic lipoamines and is attenuated by cannabigerol"** *Journal of Cachexia, Sarcopenia and Muscle* **2019**, *10*, 844-859 **(rat study)**

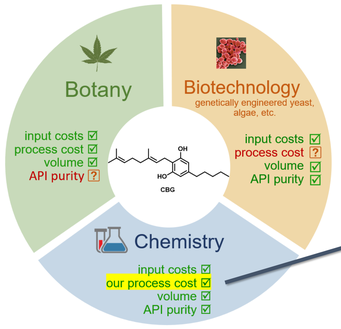
Results: CBG-based treatments may represent novel therapeutic option of chemo induced cachexia

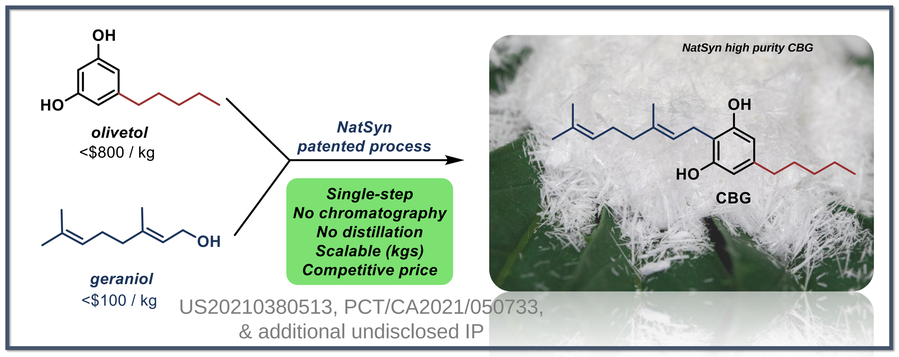
- **Significant presence in cosmetic patent space: 67 patents ---** inflammatory skin diseases, scar treatment, acne

Accessing Minor Cannabinoids

Current technology, problematic hurdles, and the *NatSyn solutions*

Options for the bulk manufacture of CBG

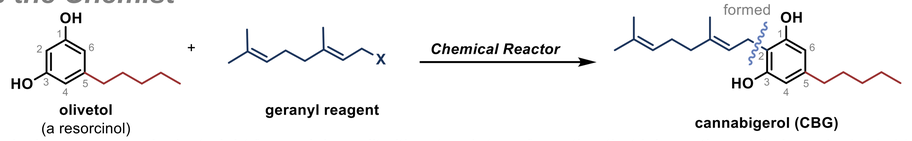




US20210380513, PCT/CA2021/050733, & additional undisclosed IP

Our one-step process solves the long-standing chemical selectivity problem

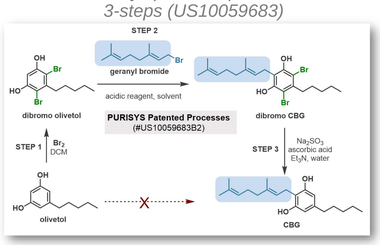
Nature vs the Chemist

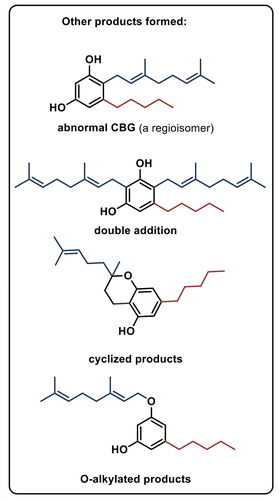


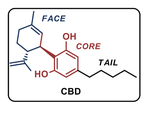
While this chemical reaction may look straight forward, in reality it's a tough transformation that inherently results in undesired side-products *(right)*. This was the main hurdle preventing cheap and easy synthesis of cannabinoids. ***Not anymore!***

	CBG	Abnormal CBG
Nature's geranyl transferase enzymes	100	0
All previous Lewis and Bronsted acids	minor	major
Our Naturally Synthetic Inc. process	80	20

First solution to correcting chemical selectivity
Purisys patented process:
3-steps (US10059683)

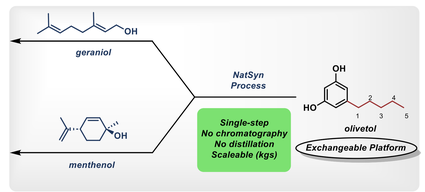


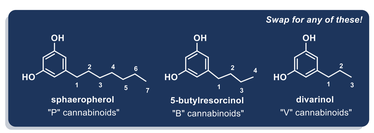




CORE	TAIL	FACE: cannabidiol	Δ9-THC	cannabigerol	cannabinol	Δ8-THC	cannabichromene	cannabielsoin	cannabicyclol
regular	"P"	CBDP	THCP	CBGP	CBNP	Δ8-THCP	CBCP	CBEP	CBLP
regular	regular	CBD	THC	CBG	CBN	Δ8-THC	CBC	CBE	CBL
regular	"B"	CBDB	THCB	CBGB	CBNB	Δ8-THCB	CBCB	CBEB	CBLB
regular	"V"	CBDV	THCV	CBGV	CBNV	Δ8-THCV	CBCV	CBEV	CBLV
"acid A"	"P"	CBDPA	THCPA	CBGPA	CBNPA	Δ8-THCPA	CBCPA	CBEPA	CBLPA
"acid A"	regular	CBDA	THCA	CBGA	CBNA	Δ8-THCA	CBCA	CBEA	CBLA
"acid A"	"B"	CBDBA	THCBA	CBGBA	CBNBA	Δ8-THCBA	CBCBA	CBEBA	CBLBA
"acid A"	"V"	CBDVA	THCVA	CBGVA	CBNVA	Δ8-THCVA	CBCVA	CBEVA	CBLVA

*Our process is a **platform technology** that involves swapping out the starting resorcinol reagent to access **all** known natural cannabinoids!*





Acknowledgements: Naturally Synthetic Inc. was founded in 2021 as a spin-off from the Magolan Lab at McMaster University. Research in the Magolan Lab at McMaster benefits from generous support from these organizations:

Michael G. DeGroote Centre for Medicinal Cannabis Research · NSERC CRSNG · David Braley Centre for Antibiotic Discovery · Michael G. DeGroote Institute for Infectious Disease Research · INNOVATION.CA Canada Foundation for Innovation / Fondation canadienne pour l'innovation · McMaster University