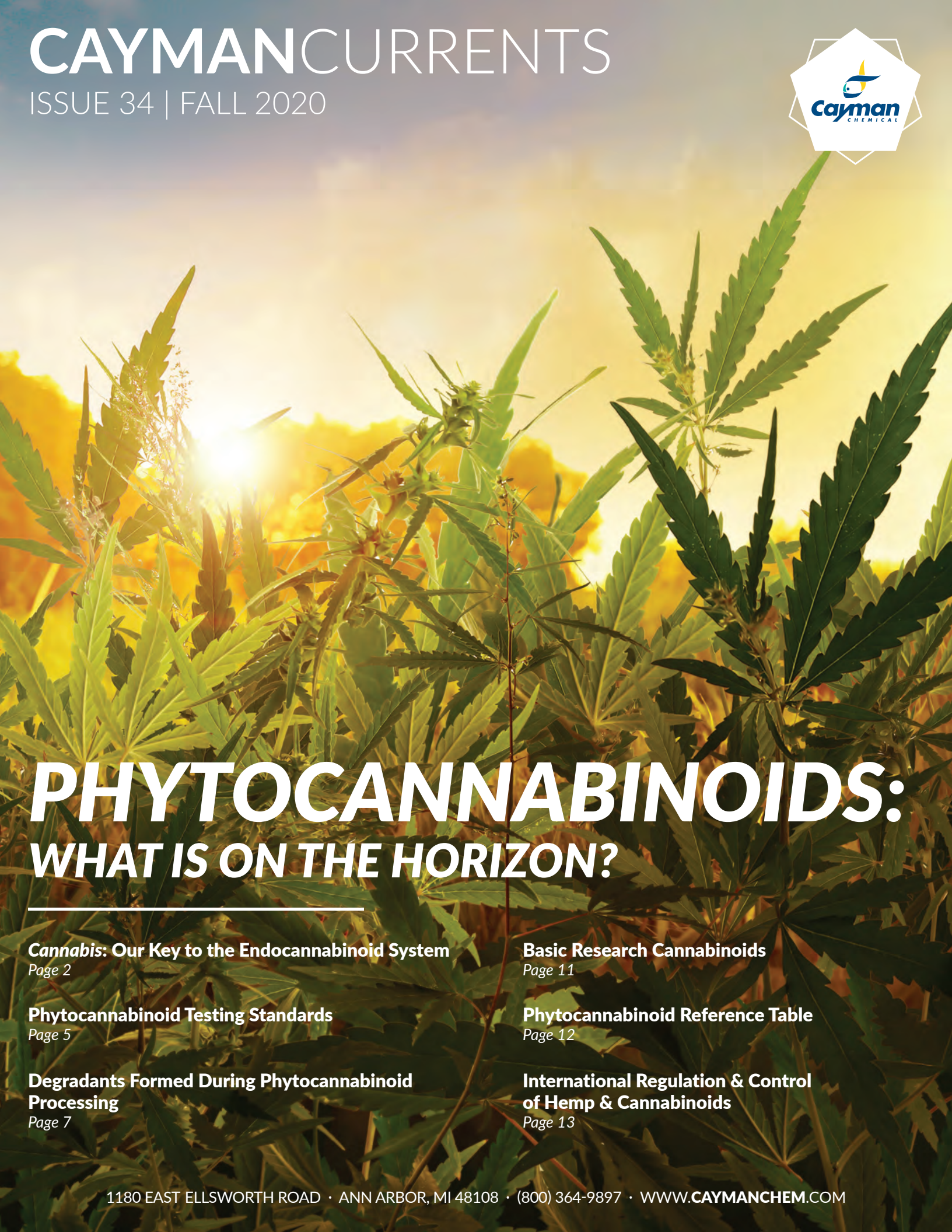
CAYMANCURRENTS
ISSUE 34 | FALL 2020



PHYTOCANNABINOIDS:
WHAT IS ON THE HORIZON?

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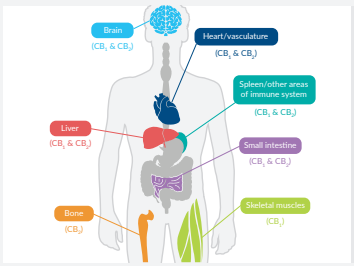
DEVELOPMENTS IN RESEARCH, TESTING, & LEGISLATION

As Δ^9-THC remains a controlled substance in almost all countries, new avenues are opening for the other non-regulated *Cannabis* constituents. Much is still left to be uncovered in knowing how *Cannabis* stimulates the endocannabinoid system in the body and to substantiate its anecdotal and scientific merits as a potential therapeutic. Cayman continues to keep an eye on the horizon by supporting law enforcement agencies in the quick identification of illicit synthetic cannabinoids, legal *Cannabis* industry purveyors in the safe manufacture of their products, and basic science researchers in the pursuit of understanding the endocannabinoid system and how it is affected by *Cannabis*.

Our analytical reference standards and ISO 17034-produced Certified Reference Materials can be used to identify and quantitatively measure the components found in *Cannabis* including terpenes, degradants, and contaminants such as mycotoxins, pesticides, and residual solvents.



Our broad collection of assay kits, antibodies, enzymes, and ligands can be used to study cannabinoid receptor signaling, the enzymes involved in endocannabinoid synthesis and degradation, the transporters that enable cellular uptake/release, and the activity of many metabotropic, nuclear, and ionotropic receptors that also recognize cannabinoids as ligands.

Our comprehensive contract services offer decades of industry expertise in assay and methods development, sample preparation, and analysis of endocannabinoids in biological samples. Rapid custom synthesis of high-purity reference standards is also available.

Cannabis: Our Key to the Endocannabinoid System

Ben Euhus, M.Sc.
Cannabis Science Researcher and Educator

The *Cannabis sativa* plant has seen a tremendous amount of notoriety over the last few decades due to an increasing support of legalization. After a century-long prohibition, researchers, doctors, and legislatures are beginning to peel back the uncertainty of one of civilization's oldest plant companions.[1] *Cannabis* has been recreationally and medicinally consumed farther back than recorded history. Although today, we still know very little about it. Its powers come from the ability of the chemical constituents to activate and affect the endocannabinoid system (ECS), a homeostatic regulatory system ubiquitous to every living creature on the planet.[1] Today, *Cannabis* is used in a variety of countries worldwide, but due to restricted access to research, our understanding of its therapeutic potential and limitations are not fully realized. Over the last few decades, more inquiries have been made in understanding the ECS and *Cannabis'* role as a therapeutic agent, and although beneficial for numerous therapeutic scenarios, there are indications that its efficacy is not consistent across all disease types.

> Whole *Cannabis* extracts work more effectively than isolated cannabinoids, and not every *Cannabis* variety, or chemovar, is created equally.

Cannabis is the evolutionary byproduct of a plant that evolved to affect the ECS, a biological system of receptors, ligands, and enzymes stemming back to aquatic species 400 million years before the arrival of plants and trees.[2] The human body is constantly producing endogenous cannabinoids—endocannabinoids. In the lab, *Cannabis* led us to the ECS, but in nature the ECS was responsible for *Cannabis*. *Cannabis* is a mixture of over 500 compounds.[3] Most notable are compounds from three categories: phytocannabinoids (such as Δ^9-THC and CBD), terpenoids, and flavonoids.[3] Phytocannabinoids like Δ^9-THC and CBD affect the body through their activities on G protein-coupled receptors such as cannabinoid receptor 1 (CB_1) and cannabinoid receptor 2 (CB_2) as well as GPR55. Although, there is growing evidence for related receptors affected by cannabinoids such as the transient receptor potential (TRP) channels and peroxisome proliferator-activated receptors (PPARs) that has largely gone unnoticed by the general public (**Figure 1**).[1] Both TRP and PPAR receptors have a pronounced role in many bioregulatory pathways. For example, TRPV1 is notorious for its role in the regulation of body temperature as well as the sensations of heat and pain. PPARγ is expressed in almost all tissues and is essential for pathways involved in cellular differentiation and development.

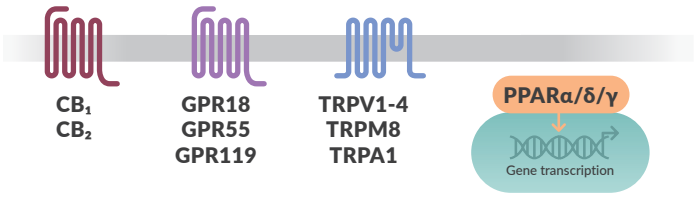


Figure 1. Extended endocannabinoid system of receptors activated by endo- and phytocannabinoids.

In vivo and *in vitro* evidence has demonstrated isolated cannabinoids' and whole *Cannabis* extract's ability to induce apoptosis in cancerous cells and act as a therapeutic agent in other chronic diseases.[4] Multiple pharmaceuticals containing cannabinoids or synthetic cannabinoid compounds have been released. The most recent one, Epidiolex®, is the first FDA-approved *Cannabis*-derived pharmaceutical containing just one active ingredient: CBD derived from *Cannabis*. Many states and countries are beginning to open medical marijuana programs, but our understanding of *Cannabis*' effects is a much simpler view than the actual reality.

The most glaring observations: whole *Cannabis* extracts work more effectively than isolated cannabinoids, and not every *Cannabis* variety, or chemovar, is created equally. These two observations are due to a phenomenon known as the 'entourage effect,' which is created when cannabinoids and other *Cannabis* compounds, such as terpenoids and flavonoids or other cannabinoids, are found in the presence of one another to create a potentially varied effect.[3] Its mechanisms are not fully understood and the major bioactive compounds inside of *Cannabis* have yet to be fully pinpointed, but due to different genetics and growth conditions, multiple varieties exist leading to a multitude of different possible outcomes. The varied ability of *Cannabis* chemovars was identified in a screening using a collection of 12 different whole *Cannabis* extracts for their ability to induce cell death in cancerous cell lines (**Figure 2**).

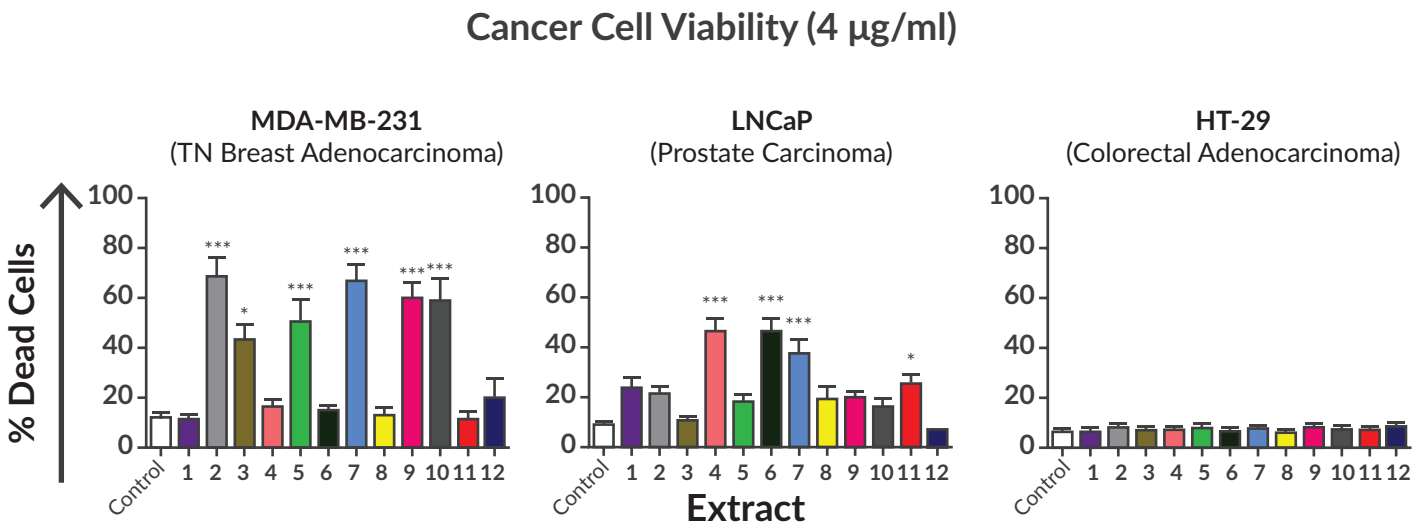


Figure 2. Cell viability of three cancerous cells against 4 µg/ml of 12 whole *Cannabis* extracts of varying cannabinoid concentrations after 24 hours of treatment as described in Baram, *et al.*[5] Image used under CC BY 3.0.

In the three cases shown in the figure, a few clear points can be made, namely that not every tissue type is affected by *Cannabis*, not every chemovar is created equal, and in some cases, the chemovars best at inducing cell death in one cancer type were ineffective with others.

This can be further highlighted in a comparative study focusing on one of the major bioactive compounds in *Cannabis*, Δ⁹-THC. In an *in vitro* study using 14 extracts containing at least 18% Δ⁹-THC and purified Δ⁹-THC, it was found that the whole *Cannabis* extracts were better at inducing cell death in A549 cancerous lung cells (**Figure 3**).

After 24 hours, 4 µg/ml of extract was enough to induce cell death with several extracts. Of the 14 extracts tested, three were able to bring cancerous cell levels down at least 50%, one of which achieved 80% cell death. This is in direct contrast with the performance of purified Δ⁹-THC.

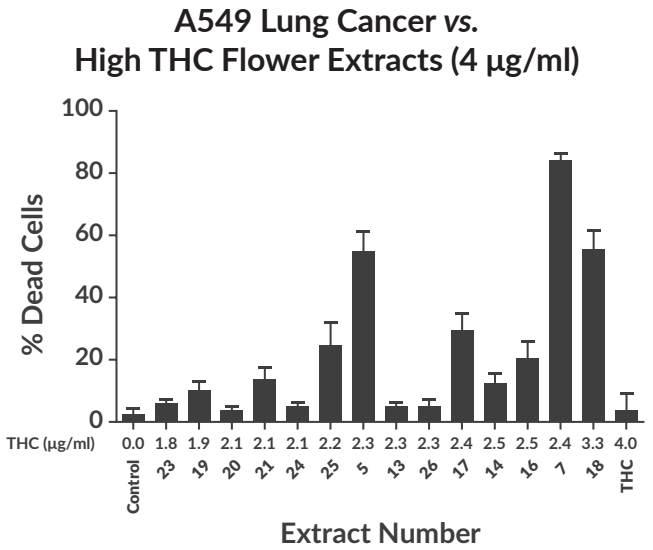
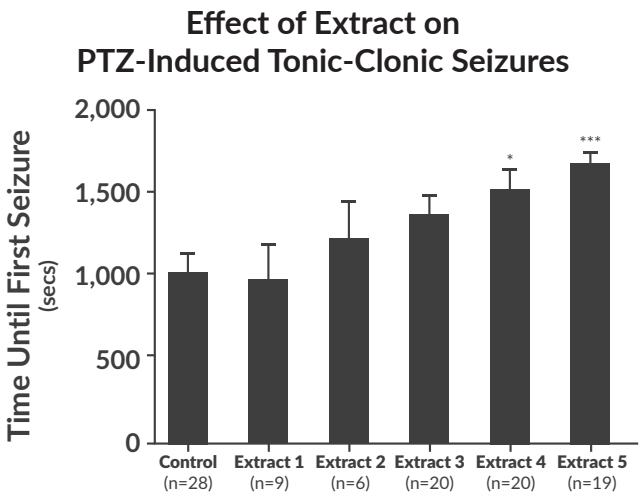


Figure 3. Cell viability of A549 lung cancer cells against 4 µg/ml of 14 high Δ⁹-THC whole *Cannabis* extracts after 24 hours of treatment as described in Baram, *et al.*[5] Image used under CC BY 3.0.

Additionally, Δ⁹-THC content in the high Δ⁹-THC extracts did not seem to correlate to its performance, indicating an increased activity from additional bioactive compounds.

The same trends can be seen using high CBD plants. In an *in vivo* investigation, five high CBD plants with roughly the same concentration of CBD and Δ⁹-THC (50% and 2%, respectively) were investigated for their therapeutic ability to treat symptoms of epilepsy (**Figure 4**). All five extracts



	% of Mice Developing Seizures	% Survival
Control	**75**	**46.4**
Extract 1	**66.7**	**88.9**
Extract 2	**50**	**87.5**
Extract 3	**45**	**95**
Extract 4	**35**	**85**
Extract 5	**21.5**	**100**

Figure 4. Effect of equally high CBD *Cannabis* strain extracts on pentylenetetrazole (PTZ)-induced convulsions as described in Berman, *et al.*[6] Image used under CC BY 4.0.

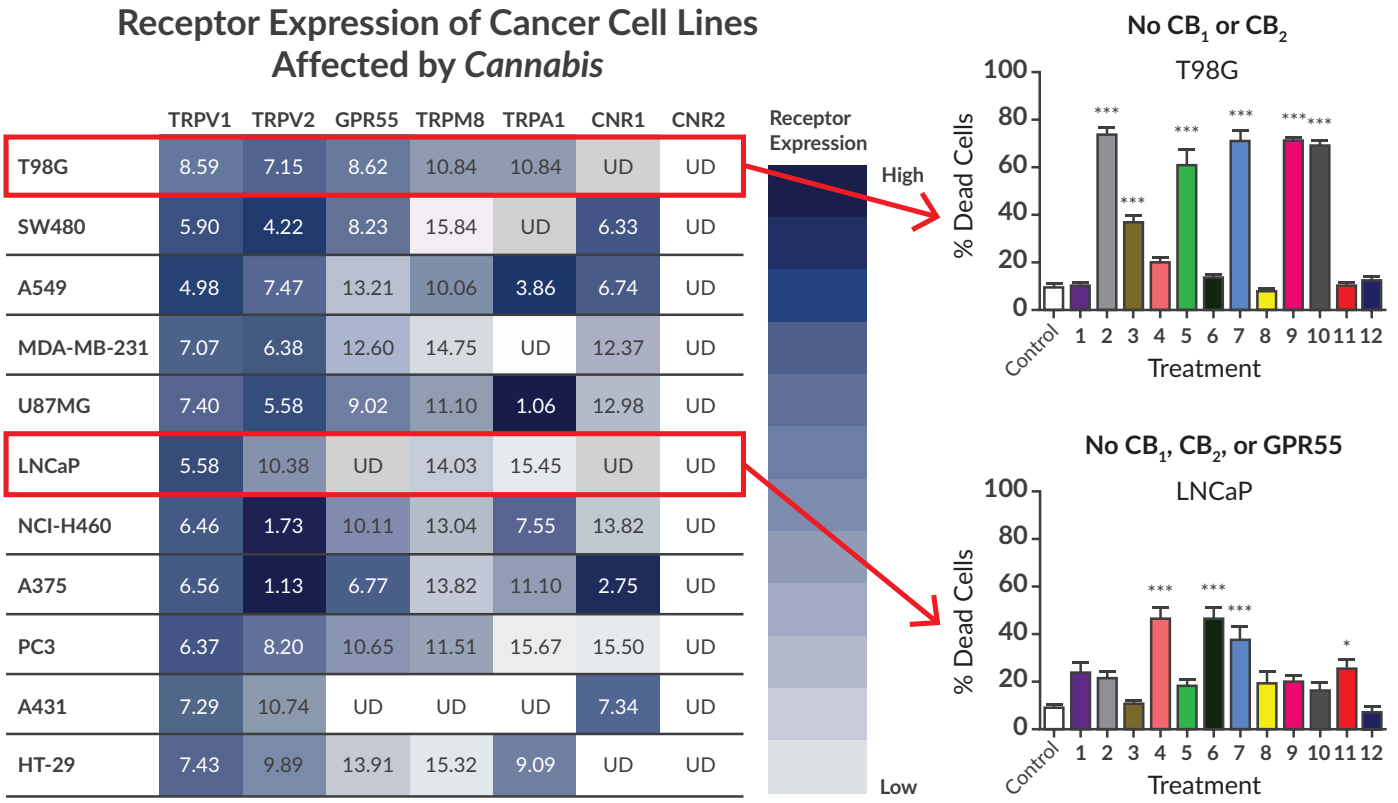


Figure 5. Cannabimimetic receptors TRPV1, TRPV2, GPR55, TRPM8, and TRPA1 along with CNR1 (CB_1) and CNR2 (CB_2) mRNA levels were evaluated by qPCR. Expression levels were represented as ΔCT levels of the receptors as described in Baram, *et al.*[5] UD - under detectable level. Image used under CC BY 3.0.

were roughly the same in what would be considered their major bioactive compounds, Δ^9-THC and CBD, but their outcomes were extremely varied. Currently throughout the world, the testing of the concentration of compounds inside of *Cannabis* only covers a fraction of the entire plant. Most regulatory groups only require the Δ^9-THC and CBD levels to be publicly addressed, while biological studies show there is in fact much more involved.

The therapeutic potential of *Cannabis* and its constituents will never be fully realized until bioactive compounds are identified, or more in-depth testing is commonplace. Additionally, the scope of our outlook on the ECS is limiting. When observing outcomes strictly based on interactions with CB_1 and CB_2, we are ignoring the actual basis for mechanisms. Of the cancerous cell lines noted by Baram, *et al.*, two that were susceptible to *Cannabis* had no detectable expression of CB_1 or CB_2 (**Figure 5**).[5] LNCaP had neither CB_1, CB_2, nor GPR55 (**Figure 5**).

The utilization of *Cannabis* has a long way to go before reaching perfection, but it does contain compounds that make promising therapeutic agents for certain conditions. With a wider view of the ECS beyond just CB_1 and CB_2, and an understanding that a chemovar's abilities are outside of just Δ^9-THC and CBD, we would be better able to address and manipulate cannabinoid-based therapies.

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ABOUT THE AUTHOR

Ben Euhus, M.Sc.

Mr. Euhus is a *Cannabis* researcher and educator who trained at the Technion in Haifa, Israel under Dr. David Meiri, working to further the current understanding of the endocannabinoid system and the therapeutic role of *Cannabis* in cancer and other chronic illnesses. His research revolved around the biological mechanics of *Cannabis* after ingestion and its beneficial effects in chronic neural disease management.

CERTIFIED REFERENCE MATERIALS FOR

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Phytocannabinoid Mixtures (CRMs)

Analytes Included in Mixtures & Offered as Single Standards	Mixture 11 *(Item No. 21306)*	Mixture 10 *(Item No. 21305)*	Mixture 6 *(Item No. 25077)*	Mixture 5 *(Item No. 25076)*	Mixture 3 *(Item No. 23251)*
CBD	✓	✓	✓	✓	✓
Δ^9-THC	✓	✓	✓	✓	✓
CBN	✓	✓	✓	✓	✓
THCA-A	✓	✓	✓	✓	
CBDA	✓	✓	✓	✓	
CBG	✓	✓	✓		
CBC	✓	✓			
CBDV	✓	✓			
CBGA	✓	✓			
Δ^8-THC	✓	✓			
THCV	✓				

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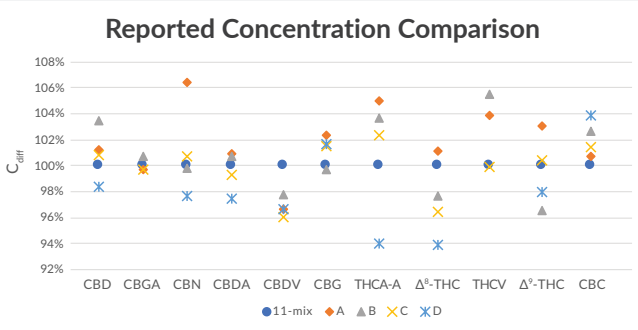

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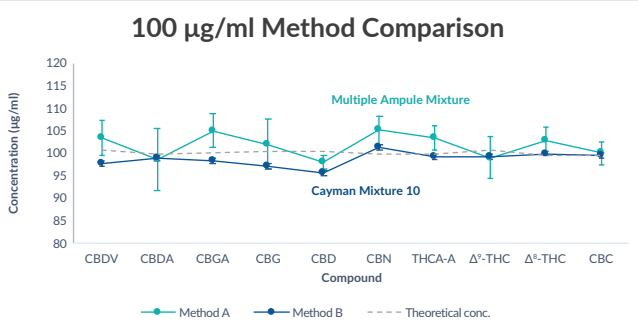
We compared two methods to generate a standard curve to quantitate 10 prevalent phytocannabinoids and found that pre-made CRM mixtures improve efficiency and eliminate pipetting errors.



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Degradants Formed During Phytocannabinoid Processing

Katrina J. Holly, Jeffrey B. Williams, M.Sc., and Kirk W. Hering, Ph.D., Cayman Chemical

Cannabis is extremely complex, being comprised of several hundred chemical constituents that contribute to its psychoactive as well as medicinal properties. Over the past several decades, scientists have sought to identify and characterize these compounds to better understand the plant's bioactivity. Many of these compounds, native to the plant itself, have been termed phytocannabinoids. Two of the most well-known phytocannabinoids are Δ^9-THC and CBD. (Note: Cayman uses the dibenzopyran numbering system common in today's literature for Δ^9-THC and other tetrahydrocannabinols.[1]) Δ^9-THC has been shown to be primarily responsible for the psychoactive nature of marijuana, resulting in the "high" experienced from smoking, vaping, or ingestion. CBD, on the other hand, is not psychoactive and has been found to have anti-inflammatory and pain-reducing activity in addition to other beneficial properties.

Extraction and isolation of phytocannabinoids from *Cannabis* inflorescences (flowers) requires extensive processing. During various stages of plant processing, many phytocannabinoids may undergo degradation through isomerization and/or oxidation. Formation of these byproducts can complicate the isolation of the desired phytocannabinoids and also degrade pure isolates over time if they are improperly stored. The pharmacological activities of these byproducts are not well understood due to the limited investigations performed. Identification of these phytocannabinoid degradation byproducts and the conditions under which they form may lead to more robust extraction and isolation methods, providing higher quality *Cannabis* products.

Biosynthetic Background

The most common phytocannabinoids consist of a resorcinolic acid core with an isoprenyl moiety positioned *para* to a pentyl chain.[1] They are derived from an olivetolic acid precursor, which then undergoes enzymatic transformation into cannabigerolic acid (CBGA) and then cyclization *via* specific synthases to form cannabichromenic acid (CBCA), cannabidiolic acid (CBDA), and Δ^9-tetrahydrocannabinolic acid A (Δ^9-THCA-A) (**Figure 1**).[1] However, these phytocannabinoid acids are not particularly stable. They decarboxylate rapidly when heated but also gradually decarboxylate over time, even under ambient conditions.[1,2] Such decarboxylation commonly occurs when *Cannabis* is smoked or during the extraction process, converting the non-psychoactive Δ^9-THCA-A to the psychoactive Δ^9-THC.[2] The corresponding neutral

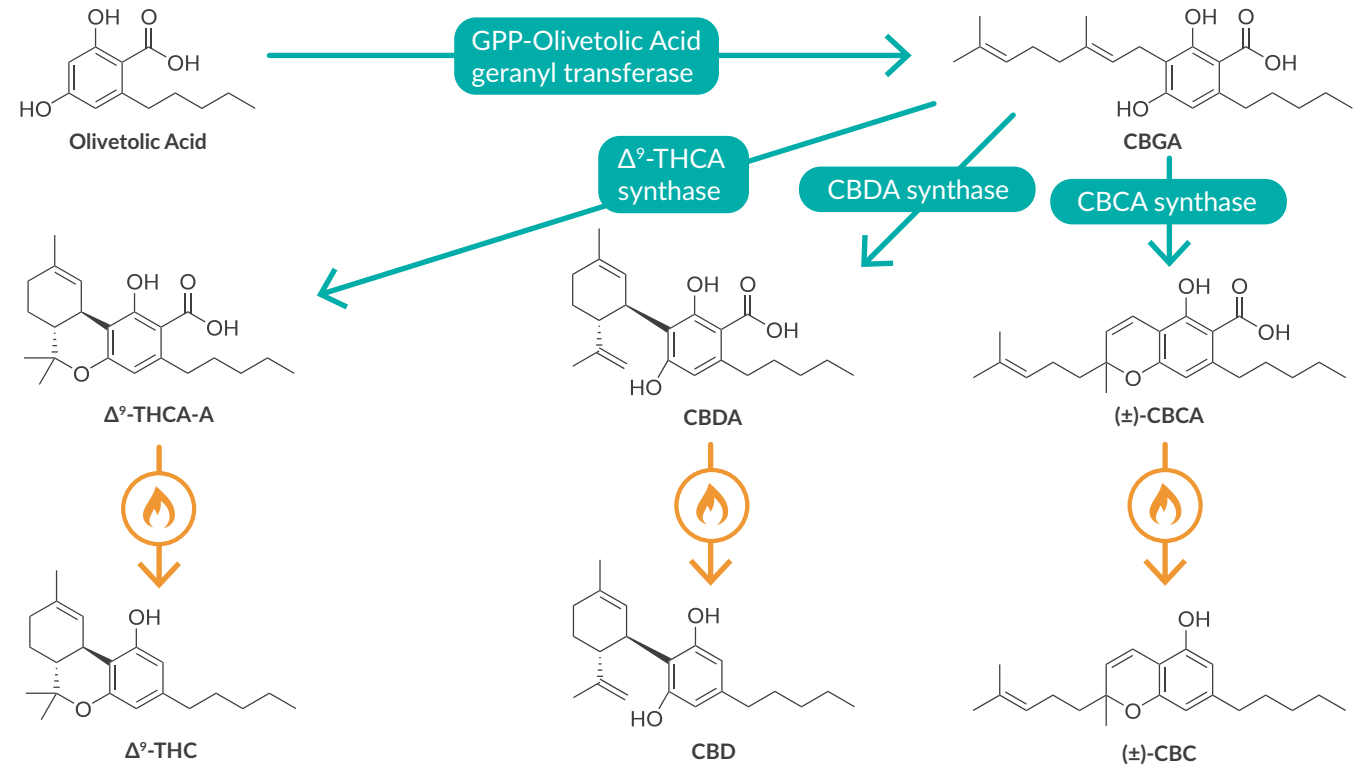

Figure 1. Biosynthesis of phytocannabinoid acids in *Cannabis* begins with a common precursor called olivetolic acid that then undergoes a series of enzymatic transformations. When exposed to heat, the phytocannabinoid acids readily decarboxylate into their neutral forms.

phytocannabinoids that result from decarboxylation are the most commonly isolated and studied *Cannabis* constituents.

Processing

The process of extracting phytocannabinoids from *Cannabis* inflorescences is both time- and labor-intensive work. While each processor may follow a different method to obtain *Cannabis* extracts, the overall model of harvest, extraction, winterization, filtration, and distillation has been shown to provide isolated material with >90% phytocannabinoid content. After harvesting, *Cannabis* inflorescences are dried and removed from the harvested plant material. At this point some extractors choose to decarboxylate the acidic phytocannabinoids by oven-drying them at temperatures >125°C prior to solvent extraction. The plant matter is then extracted with solvents such as butane, ethanol, or supercritical fluid carbon dioxide. The biomass extract is cooled in a process known as winterization to induce lipid solidification, which is then removed by filtration. If necessary, the extract may be subjected to additional filtrations through clays or other solid support filter aids. Finally, the extract is vacuum distilled at very low vapor pressures and high temperatures, where decarboxylation occurs if it has not already. The lack of uniformity in standard operating procedures for the extraction and distillation processes provides multiple pathways for forming phytocannabinoid byproducts. For example, it is suspected that the acidic or basic nature of various filtration media may be responsible for byproduct formation.[3] Additionally, the heating required for distillation increases the potential formation of byproducts through oxidative degradation. Identification of these byproducts provides a necessary quality control check for the extraction and distillation processes to avoid byproduct contamination.

Isomerization Degradants

Under basic conditions, the double bond in Δ^9-THC isomerizes from the Δ^9 to the Δ^{10} position, becoming conjugated to the resorcinol core.[1,4] This can form two different diastereomeric structures of Δ^{10}-THC: (6a*R*,9*R*)-Δ^{10}-THC and (6a*R*,9*S*)-Δ^{10}-THC (**Figure 2**). Neither seems to exhibit any abnormal behavioral effects according to animal studies.[5] Under acidic conditions, CBD cyclizes to Δ^9-THC and further to Δ^8-THC, due to it being the more thermodynamically stable isomer (**Figure 2**). Δ^8-THC exhibits similar pharmacological effects to Δ^9-THC on the CB_1 and CB_2 receptors, except with less potency.[1] Acidic conditions also drive the double bond of either Δ^{10}-THC diastereomer to isomerize further to the $\Delta^{6a,10a}$ position.[4] This results in the formation of two potential enantiomers: 9(*R*)-$\Delta^{6a,10a}$-THC and 9(*S*)-$\Delta^{6a,10a}$-THC (**Figure 2**). Animal studies involving these two compounds revealed that the (*S*)-enantiomer produces a Δ^9-THC-like behavioral effect and that the (*R*)-enantiomer produces no noticeable effects.[5] Binding assays have shown that while both enantiomers exhibit partial agonist activity at the CB_1 and CB_2 receptors, the potency of the (*S*)-enantiomer is six times that of the (*R*)-enantiomer.[6]

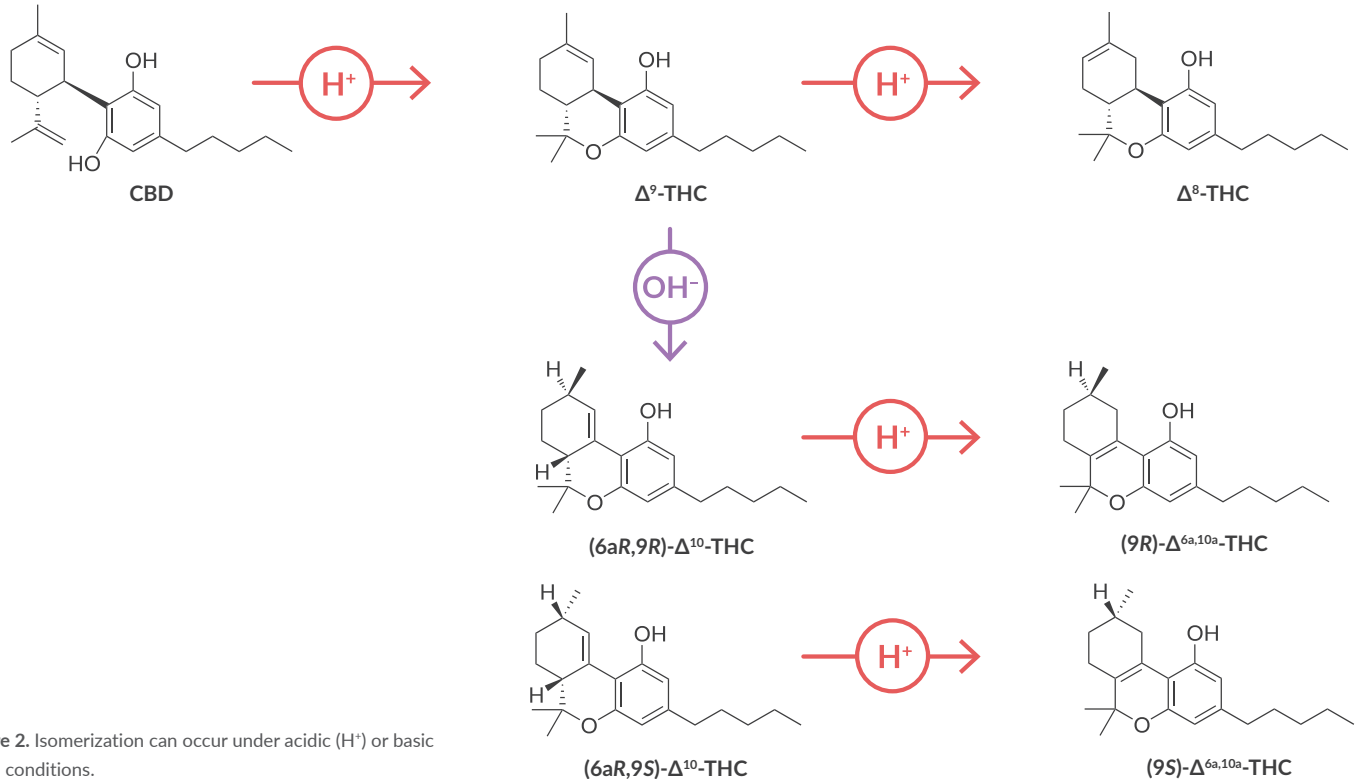

Figure 2. Isomerization can occur under acidic (H^+) or basic (OH^-) conditions.

Oxidative Byproducts

Some phytocannabinoids can be altered upon exposure to oxygen, generating various oxidative byproducts. Cannabinol (CBN) forms as the oxidative byproduct of Δ^9-THC (**Figure 3**).[1,7] Studies have shown that Δ^9-THC oxidation occurs at a rate of up to 5% loss per month at room temperature.[1] However, the rate of CBN formation is not equal to the oxidative degradation rate of Δ^9-THC.[7] This seemingly missing Δ^9-THC could be explained due to the proposed presence of hydroxylated and epoxidized intermediates generated during the Δ^9-THC oxidation process.[1] Additionally, formation of Δ^8-THC may account for part of the Δ^9-THC loss as it can also be generated from Δ^9-THC oxidatively.[1] CBN exhibits very mild psychoactivity when compared to Δ^9-THC.[2] A heat map of the relative potency of various isomers is depicted in **Figure 4**.

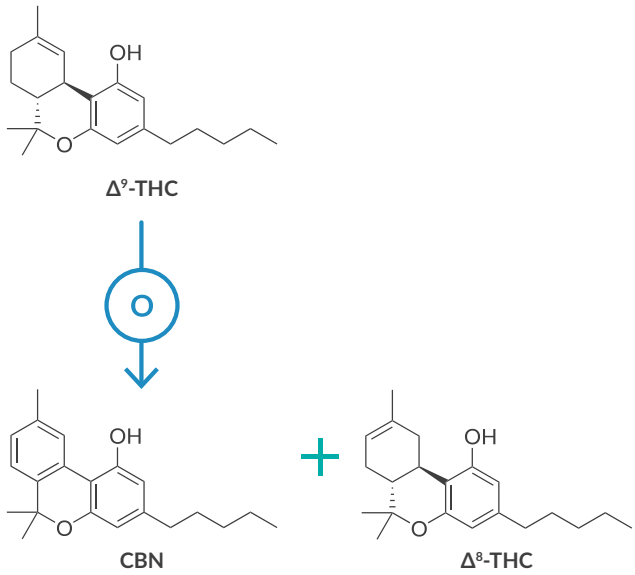

Figure 3. Atmospheric oxygen oxidizes Δ^9-THC to CBN and Δ^8-THC, as well as to other intermediates not shown above.

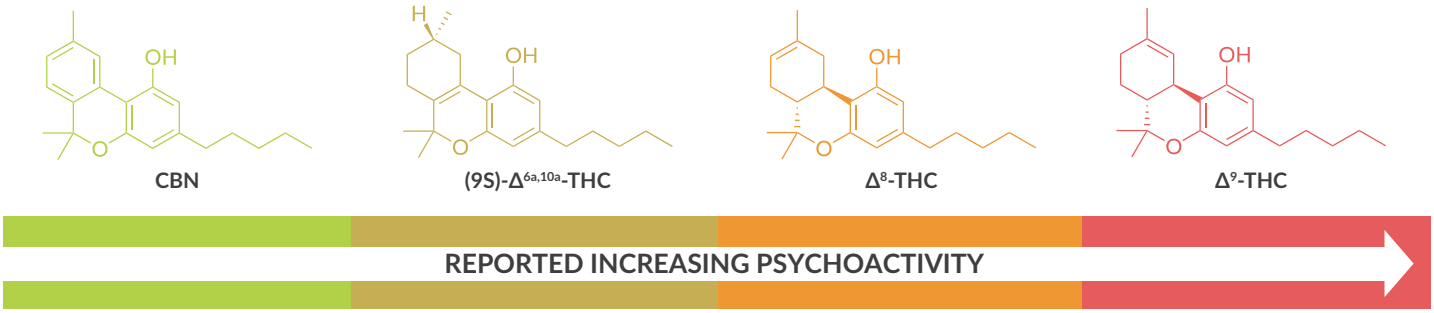

Figure 4. Reported psychoactivity displayed in relative terms of potency.

In the presence of ultraviolet light, (±)-cannabichromene (CBC) undergoes [2+2] cycloaddition to form (±)-cannabicyclol (CBL) (**Figure 5**). Formation of CBL is based on the concentration of CBC and may serve as a marker for storage in the presence of light. Currently, no pharmacological data is available concerning the bioactivity of CBL.

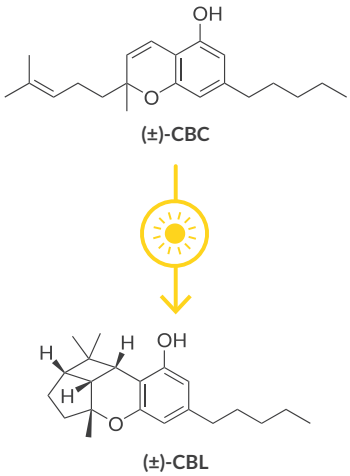

Figure 5. Photo-oxidation induces a [2+2] cyclization in (±)-CBC, resulting in (±)-CBL.

Under pyrolytic conditions such as smoking, CBD is oxidized to cannabielsoin (CBE) (**Figure 6**).[1,8] However, in rare instances, the carboxylic acid CBEA has been reportedly isolated from hashish, suggesting that some other form of degradation to CBE or CBEA may be possible.[9] Currently, little pharmacological data exists concerning the bioactivity of CBE.

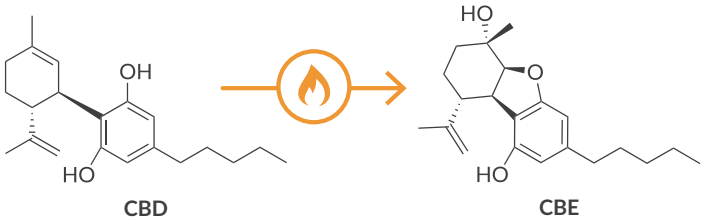

Figure 6. Pyrolysis of CBD leads to the oxidative formation of CBE.

Phytocannabinoid Reference Table

Flip to page 12 to find a list of known phytocannabinoid compounds and their abbreviations sorted by molecular weight.

Another oxidative series of phytocannabinoid byproducts is the richly colored quinone series. Phytocannabinoid quinones are designated with a "Q" and include those formed from CBD, CBN, Δ^9-THC, Δ^8-THC, (±)-CBC, and CBG (**Figure 7**).

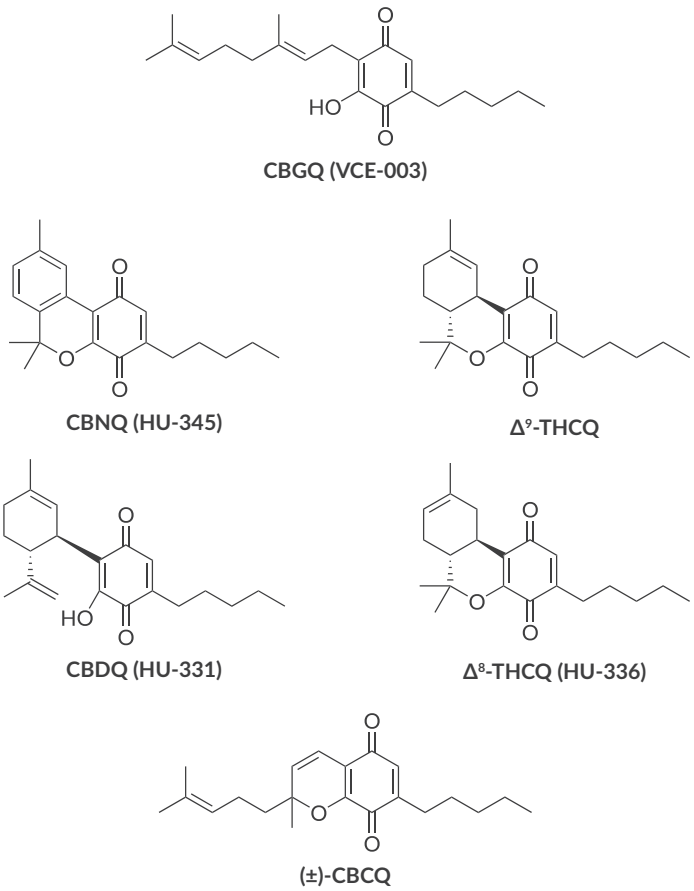

Figure 7. Common phytocannabinoid quinones.

A forensic technique known as the Beam test utilizes the oxidative conversion of CBD to CBDQ, better known as HU-331, to detect the presence of *Cannabis* through treatment with a base to reveal a deep purple color (**Figures 8 & 9**).[10] The Beam test conditions are typically selective for phytocannabinoids with two free hydroxyls on the resorcinol ring system. Other phytocannabinoid quinones are also known to be highly colored species and may be formed by alternative oxidative mechanisms. Scientists have been able to form Δ^9-THCQ through electrochemical oxidation, but there is still the need for development of a reliable assay that can conveniently confirm the presence of Δ^9-THC in a sample through rapid conversion to Δ^9-THCQ.[11] Some phytocannabinoid quinones have been found to have medicinal properties. Pharmacological research conducted into the quinone series thus far has revealed anticancer potential for HU-331, Δ^8-THCQ (HU-336), and CBNQ (HU-345), as well as anti-inflammatory potential for CBGQ (VCE-003).[1,12]

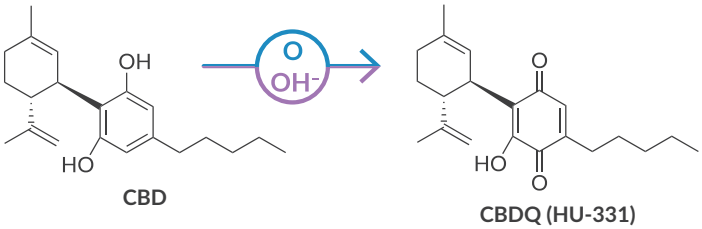

Figure 8. Oxidation of neutral phytocannabinoids can generate their respective quinone species. The conversion of CBD to CBDQ is facilitated through the Beam test utilizing base-catalyzed oxidation.

Figure 9. Left to right: CBD before Beam test; HU-331 after Beam test; crystalline HU-331.

Conclusion

The field of phytocannabinoid testing and research is experiencing rapid growth mainly resulting from the USDA Farm Bill legalization of regulated hemp products and from other changes to legalization at the state level. Many of these degradant byproducts have unknown or incomplete studies on their pharmacological and toxicological effects. Identification of these byproducts and a better understanding of the chemistry involved in their formation is paramount to providing the highest quality *Cannabis* products.

Read more about the international regulation and control of hemp and cannabinoids on page 13 of this issue.

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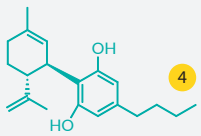
BASIC RESEARCH CANNABINOIDS

Synthetic compounds for understanding cannabinoid chemistry and signaling

Novel Four- and Seven-Carbon Phytocannabinoids

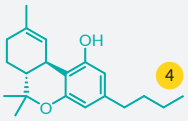
Research published in *Nature Scientific Reports* identified two new homologs of CBD and Δ^9-THC while analyzing the chemical composition of a hemp extract. Four-carbon homologs, CBDB and Δ^9-THCB, and seven-carbon homologs, CBDP and Δ^9-THCP, were named. Alkyl side chain length is incredibly important for interaction with human cannabinoid receptors CB_1 and CB_2 as it directly correlates with receptor binding affinity. These new compounds are reported to have binding activity more potent than that of Δ^9-THC and could account for the pharmacological properties of some *Cannabis* varieties, making the need to identify their presence imperative to the *Cannabis* industry.



CBDB

Cannabidibutol

Available as Item No. 29031



Δ^9-THCB

Δ^9-Tetrahydrocannabibutol

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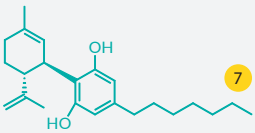

CBDP

Cannabidiphorol

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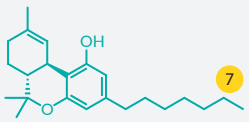

Δ^9-THCP

Δ^9-Tetrahydrocannabiphorol

Available as Item No. 30171

READ THE ARTICLE: Why Does Alkyl Chain Length Matter?
www.caymanchem.com/alkylchain

ALSO AVAILABLE FROM CAYMAN

Phytocannabinoid Quinones

Richly colored quinones are byproducts of phytocannabinoid oxidation. Several have anticancer and anti-inflammatory potential.

Item No.	Compound	Oxidative Substrate	Pharmacological Potential
30846	(±)-CBCQ	CBC	Unknown
30862	CBGQ (VCE-003)	CBG	Antioxidant, anti-inflammatory, neuroprotective
10005673	HU-331 (CBDQ)	CBD	Anticancer, anti-angiogenic

Cannabimimetic Research Targets

Mimicking the effects of endocannabinoids or phytocannabinoids, these compounds share a similar chemical structure to Δ^9-THC.

Item No.	Compound	Receptor Target(s)	Pharmacological Potential
13218	(–)-CP 47,497 (exempt preparation)	CB_1	Analgesic
90084	(–)-CP 55,940	CB_1, CB_2, GPR55	Neuroprotective, anticancer
90083	HU-210 (exempt preparation)	CB_1, CB_2, GPR55, glycine	Anti-inflammatory, analgesic, anxiolytic, proliferative
10006350	HU-211	NMDA	Neuroprotective, anticonvulsant
90086	HU-308	CB_2	Analgesic, anti-inflammatory, immunomodulatory, proliferative, antioxidant
10005428	JWH 133	CB_2	Anti-inflammatory, neuroprotective, anticancer
10009280	L-759,633	CB_2	Anti-inflammatory, analgesic
10009195	O-2545 (hydrochloride)	CB_1, CB_2	Analgesic

PHYTOCANNABINOID REFERENCE TABLE

Use this list of known phytocannabinoid compounds and their abbreviations that is sorted by molecular weight (MW) to help you in your analytical workflow.

Abbreviation	Common Name	MW
CBV	Cannabivarin	282.4
CBCV	Cannabichromevarin	286.4
CBDV	Cannabidivarin	286.4
THCV	Δ^9-Tetrahydrocannabivarin	286.4
Δ^8-THCV	Δ^8-Tetrahydrocannabivarin	286.4
CBLV	Cannabicyclovarin	286.4
CBTV	Cannabicitravarin	286.4
CBGV	Cannabigerovarin	288.4
CBB	Cannabibutol	296.4
CBCB	Cannabichromebutol	300.4
CBDB	Cannabidibutol	300.4
Δ^9-THCB	Δ^9-Tetrahydrocannabibutol	300.4
Δ^8-THCB	Δ^8-Tetrahydrocannabibutol	300.4
CBLB	Cannabicyclobutol	300.4
CBTB	Cannabicitrabutol	300.4
CBEV	Cannabielsovarin	302.4
CBGB	Cannabigerobutol	302.5
CBND	Cannabinodiol	310.4
CBN	Cannabinol	310.4
CBC	Cannabichromene	314.5
CBD	Cannabidiol	314.5
Δ^9-THC	Δ^9-Tetrahydrocannabinol	314.5
Δ^8-THC	Δ^8-Tetrahydrocannabinol	314.5
CBL	Cannabicyclol	314.5
CBT	Cannabicitran	314.5
CBEB	Cannabielsobutol	316.4
CBG	Cannabigerol	316.5
CBNR	Cannabinerol	316.5
CBCQ	Cannabichromenquinone	328.5
CBDQ	Cannabidiolquinone	328.5
Δ^9-THCQ	Δ^9-Tetrahydrocannabinoquinone	328.5

Abbreviation	Common Name	MW
CBCVA	Cannabichromevarinic Acid	330.4
CBDVA	Cannabidivarinic Acid	330.4
THCVA	Δ^9-Tetrahydrocannabivarinic Acid	330.4
CBE	Cannabielsoin	330.5
CBGQ	Cannabigeroquinone	330.5
CBGVA	Cannabigerovarinic Acid	332.4
CBP	Cannabiphorol	338.5
CBCP	Cannabichromephorol	342.5
CBDP	Cannabidiphorol	342.5
Δ^9-THCP	Δ^9-Tetrahydrocannabiphorol	342.5
Δ^8-THCP	Δ^8-Tetrahydrocannabiphorol	342.5
CBLP	Cannabicyclophorol	342.5
CBTP	Cannabicitraphorol	342.5
CBCBA	Cannabichromebutolic Acid	344.5
CBDBA	Cannabidibutolic Acid	344.5
Δ^9-THCBA	Δ^9-Tetrahydrocannabibutolic Acid	344.5
CBGP	Cannabigerophorol	344.5
CBGBA	Cannabigerobutolic Acid	346.5
CBNA	Cannabinolic Acid	354.5
CBCA	Cannabichromenic Acid	358.5
CBDA	Cannabidiolic Acid	358.5
THCA-A	Δ^9-Tetrahydrocannabinolic Acid A	358.5
Δ^8-THCA-A	Δ^8-Tetrahydrocannabinolic Acid A	358.5
CBLA	Cannabicyclolic Acid	358.5
CBEP	Cannabielsophorol	358.5
CBGA	Cannabigerolic Acid	360.5
CBNRA	Cannabinerolic Acid	360.5
CBCPA	Cannabichromephorolic Acid	386.5
CBDPA	Cannabidiphorolic Acid	386.5
Δ^9-THCPA	Δ^9-Tetrahydrocannabiphorolic Acid	386.5
CBGPA	Cannabigerophorolic Acid	388.5

Download the complete reference list & find additional resources on our Hemp & Cannabis Analytical Standards page at **www.caymanchem.com/cannabistesting**

INTERNATIONAL REGULATION & CONTROL OF HEMP & CANNABINOIDS

For a plant that has been used for millennia, controls on the supply of psychoactive and non-psychoactive components extracted from Cannabis are relatively recent, with international regulations starting at the beginning of the 20th century with the Harrison Narcotics Tax Act (1914) and International Opium Conventions (1912 and 1925). Dr. Keith Williams and Sebastian Buchert, Analytical Standards Business Development Managers at Cayman, describe the current regulatory landscape with a focus on how it pertains to the manufacture and distribution of analytical reference standards for phytocannabinoids.

The earliest recorded attempt to control *Cannabis* was 1378, when Soudoun Sheikouni, the Emir of the Joneima in Arabia, prohibited *Cannabis* use.[1] He instructed that all *Cannabis* plants in the region be destroyed, and users were punished by having their teeth extracted. In the following centuries, controls were introduced by several individual countries with little international coordination until the International Opium Convention in 1912, which was not globally enacted until 1919 as part of the Treaty of Versailles.[2] The current formal controls that now apply originate from the United Nations 1961 Single Convention on Narcotic Drugs.[3] *Cannabis* and its resin were placed under Schedules I and IV, with Δ^9-THC (and selected stereoisomers) being controlled *via* Schedule I of the United Nations 1971 Convention on Psychotropic Substances. This is the primary legislation that is in force globally. However in 2019, the World Health Organisation (WHO) recommended amending the entry for *Cannabis* and *Cannabis* resin to exclude preparations of cannabidiol that are not more than 0.2% Δ^9-THC.[4]

THC Isomers Controlled by the International Narcotics Control Board

THC	THC Isomers	Stereochemical Variants
Δ^9-THC	$\Delta^{6a,10a}$-THC	7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
	$\Delta^{6a,7}$-THC	(9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
	Δ^7-THC	(6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
	Δ^8-THC	(6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
	Δ^{10}-THC	6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
	$\Delta^{9,11}$-THC	(6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

As with many natural products, there are challenges to designing and enforcing robust legislation to meet specific local needs. Any such legislation needs to take into consideration the plant material, extracts, and oils, as well as the individual active and inactive compounds from *Cannabis*. International and country-specific drug law is also covered by multiple authorities, which can result in conflict. Examples of such conflicts include federal *versus* state legislation in the US, and to a degree, the comparable situation in Europe with the European Union (EU) *versus* individual countries.

Regulations in this area are evolving rapidly and constantly changing, often focusing on the differentiation of the plant as a determining factor of regulation. In 2018, the acceptance of the Agriculture Improvement Act in the US, often referred to as the Farm Bill, removed hemp and hemp seeds from the statutory definition of marijuana so it is no longer a Schedule I controlled substance regulated by the DEA.[5] For this purpose, hemp is defined as any part of the plant containing not more than 0.3% Δ^9-THC on a dry weight basis. These changes are enabling US growers to broadly cultivate hemp and alleviating restrictions on the sale, transport, and possession of hemp-derived products, albeit through state-approved licensing.

Definition of Industrial Hemp (dry weight plant)

Country	Maximum THC Content
EU and UK	0.2%
US	0.3%
Canada	0.3%
China	0.3%
South Africa	0.3%
New Zealand	0.35%
Switzerland	1%
Thailand	1%

View a complete list of US deregulated compounds with ≤0.3% Δ^9-THC at **www.caymanchem.com/farmbill**

The removal of control status of the plant-derived materials also affects material derived synthetically, but this can be unclear and require additional clarification. Recent and proposed changes include the EU considering declaring CBD a narcotic. The United Kingdom's Food Standards Agency has stated that CBD will not be classified as such, but more likely as a novel food stuff.[6] In the US, synthetically derived tetrahydrocannabinols are still scheduled under the DEA Drug Code Number 7370.[7] For all other cannabinoids, synthetic producers need to perform additional testing to ensure that produced compounds do not contain more than 0.3% Δ^9-THC on a dry weight basis. Upon confirmation that the Δ^9-THC content meets this specification, producers can then ship compounds without the previously required regulatory controls.

This complexity increases when products are being traded internationally. Different legislative limits can result in a product being legal in one country but controlled in a second. For example, the synthetic material produced in the US outlined above may contravene EU legislation, and although the material could be exported from the US without any regulatory requirements, it is imperative to address the local competent authority to ensure that all appropriate importing regulations and requirements are met.

Control of CBD Processed Products

Country	Acceptable THC Conetent	Notes
US	0.3%	Phytocannabinoids found in hemp with ≤0.3% Δ^9-THC on a dry weight basis are excluded from DEA regulatory controls
EU, UK, and Japan	0%	Any detectable THC is likely to render the product a controlled item

Due to the international regulatory differences, accurate assessment of key components in raw material and the finished product is essential to ensure compliance. Cayman's Certified Reference Material mixtures and single-component solutions, in combination with robust analytical methodology, allow quantitative analysis of phytocannabinoid compounds to support the international trade in hemp and *Cannabis*-based products.[8]

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