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DOES THE SOURCE OF TERPENES MATTER? WHITEPAPER

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1 INTRODUCTION

Terpenes and terpenoids—also called isoprenoids—are ubiquitous throughout the botanical world. They are biosynthetic building blocks and messengers that also form the foundation of the characteristic flavors and aromas of plants and herbs. Yet, it is the presence of terpenes in cannabis that has embroiled them in heated debate.

Central to these cannabis terpene debates is whether cannabis-derived terpenes are better (or worse) than terpenes from other sources. Implicit are questions of both safety and fidelity to the cannabis plant itself. This discourse takes many familiar forms (see Table 1) and can be heard from farm to dispensary throughout the cannabis world.

TABLE 1. WHEN IS A TERPENE JUST A TERPENE?

CANNABIS-DERIVED	CRAFTED FROM OTHER SOURCES
"Natural" and therefore better	Extracting terpenes from cannabis changes them into something "gross" and potentially toxic
Capture the essence of the plant	Recreating cultivar terpene profiles from analytical data can be more true-to-plant
Terpenes derived from sources other than cannabis are "fake" or "synthetic"	Many commercially-available terpenes come from other botanicals and are also natural
Geographic and seasonal variation of cannabis-derived terpenes is a positive attribute	A specific terpene compound is the same molecule regardless of the source
	Geographic and seasonal variation of cannabis-derived terpenes is a problem to be solved

The truth is that professional and often sophisticated production methodologies are necessary before either crafted or cannabis-derived terpenes can be considered a quality option. At this early stage, purveyors of cannabis-derived terpenes often lack the tools or sophistication to produce blends that are safe, desirable, or even similar to the plant from which they come. On the other hand, formulators of crafted terpene blends face significant hurdles in teasing apart and re-creating the chemical complexity of the plant.

DID YOU KNOW?

Isoprene, the fundamental unit of all terpenes, is the most abundant hydrocarbon measured in the exhaled breath of humans with a 70 kg human producing 17 mg/day.[1,2] In terms of hot air volume, picture how much of this terpene progenitor is shared across the counter of a dispensary during a debate about cannabis.

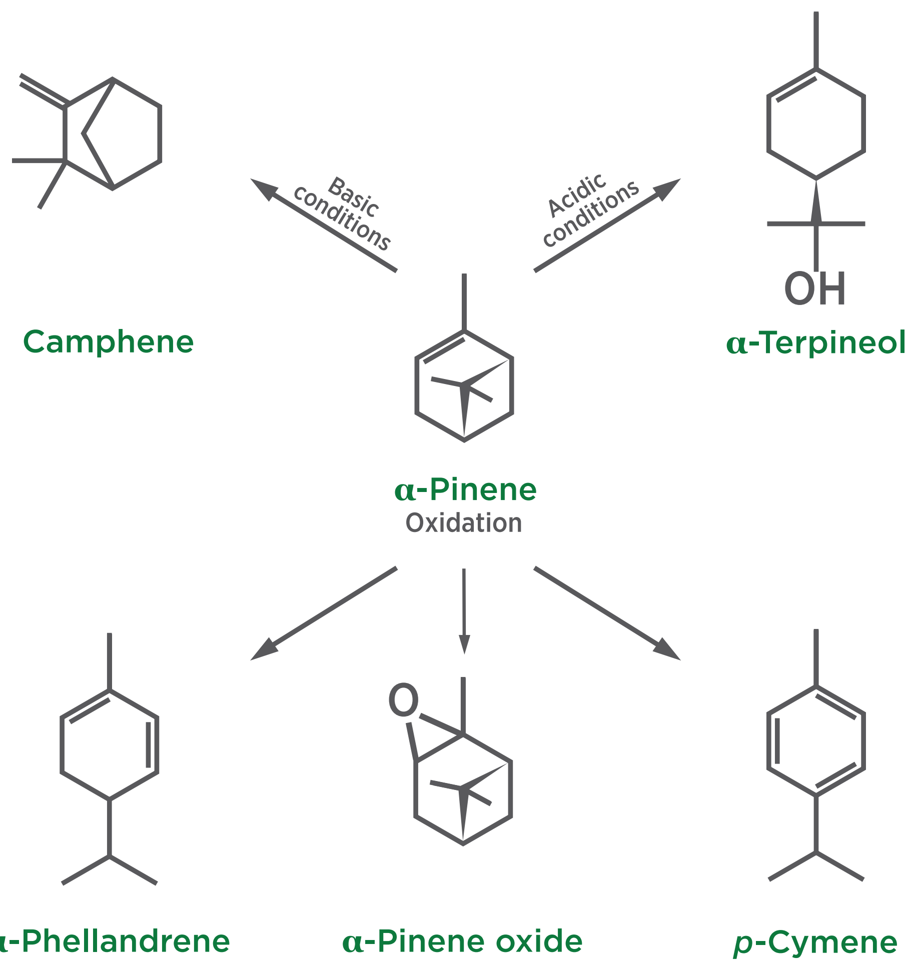
In this whitepaper we discuss scientific data that explores the nuances of terpene compositions derived from cannabis and from other sources. Upon discussing the data currently available, we offer a few educational and practical recommendations for cannabis stakeholders and consumers alike.

2 EXTRACTING CANNABIS CHANGES THE TERPENE FRACTION

No matter how delicate the extraction process, changes occur when converting plant to extract. Sometimes these changes are desirable (e.g. decarboxylation of THCA to THC), but often these changes are unwanted and can distort flavor and aromatic properties. Many cannabis extract consumers have had the experience of vaping an extract called Super Lemon Haze, only to have their taste buds tell them that it tastes nothing of the sort. Changes to the terpene fraction may even impact the so-called Ensemble Effects (cf. Entourage Effects) associated with those terpenes, causing the physiological activity of an extract to differ from that of the whole plant.

Two types of changes can occur to the terpene fraction in the course of extraction: 1) physical and 2) chemical. Physical changes alter amounts of specific terpenes relative to one another and to cannabinoids: The same plant compounds are still present, but the true-to-plant harmony is off. It's like your favorite song playing in a different key. Chemical changes alter the terpenes themselves, with one terpene turning into another (that may or may not be native to cannabis) or even something else entirely. This is like switching the words in a song; some aspects may still be familiar, but the meaning of the song has changed completely.

EXAMPLES OF CHEMICAL CHANGES



PHYSICAL CHANGES

Changes to the levels of terpenes and other light volatiles, which impact flavor, occur because higher heats, stronger vacuum and increased gas flow leads to evaporation of volatile flavor compounds along with solvent during vacuum purging. Since, relative ratios of terpenes play an important role in the complex pharmacodynamics of cannabis products, changes to these ratios can also alter the effects.[3] Maintaining the effects of the plant requires maintaining the integrity of these ratios.

Sexton and coworkers evaluated supercritical fluid extraction (SFE) with CO_2 and quantified the changes to the relative ratios of monoterpenes, sesquiterpenes, and cannabinoids throughout the process.[4] Monoterpene content decreased and sesquiterpenes increased relative to cannabinoids. Myrcene, limonene, alpha-pinene, and beta-pinene were all less concentrated in the finished extract than in the flower itself. Meanwhile THC and CBD were concentrated 3.2- and 4.0-fold, respectively. Lastly, sesquiterpenes were concentrated by factors of five to nine, effectively doubling their presence with respect to the cannabinoids. In a true-to-plant extract, all compounds would be concentrated to the same degree.

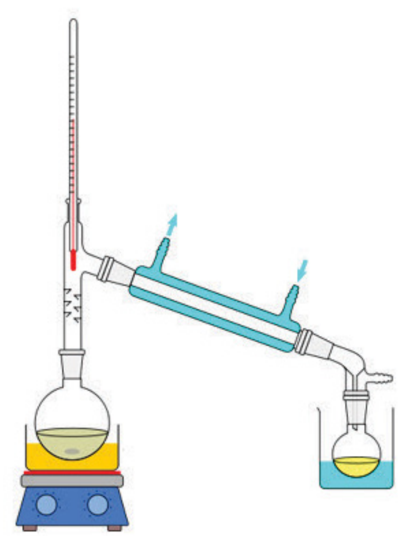
In a different study, Hazekamp and coworkers compared five different solvent extraction methods to assess the differences between the resulting extracts. They compared several Rick Simpson oil production protocols—utilizing naptha, petroleum ether, or ethanol for extraction—to two olive oil extraction methods. These researchers found an inherent tradeoff between the evaporation of residual solvents and the retention of the native terpene profile: it is typically impossible to remove all solvent without also altering terpene levels.[5]

The researchers' attempts at solvent removal—particularly higher boiling point solvents such as naptha—invariably resulted in significant evaporation of the terpene fraction. In one instance, simply placing the extract container into boiling water for just five minutes decreased its monoterpenoid content by half! Under more common solvent removal conditions (30 min. @ 145°C), levels of terpenes such as myrcene and terpinolene were diminished by greater than 95%, while ß-pinene and ß-phellandrene were rendered undetectable.[5]

EXAMPLES OF PHYSICAL CHANGES

Differential Separation

Variable Vapor Pressures

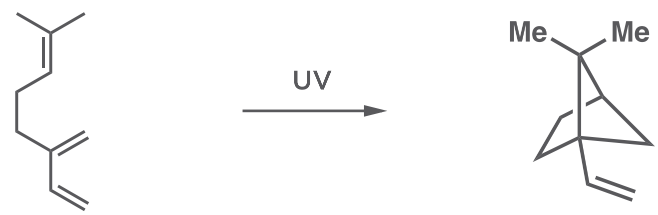


Imperfect Extraction

CHEMICAL CHANGES

While alteration of terpene ratios can impact the physiological effects of an extract, chemical changes can produce even more significant modifications. The conversion of certain terpenes into a constellation of unforeseen derivatives can expose consumers to unknown chemical mixtures with unpredictable compositions, effects, and safety profiles. In the worst cases, these changes can unintentionally create a strange brew of compounds unlike anything found in the plant.

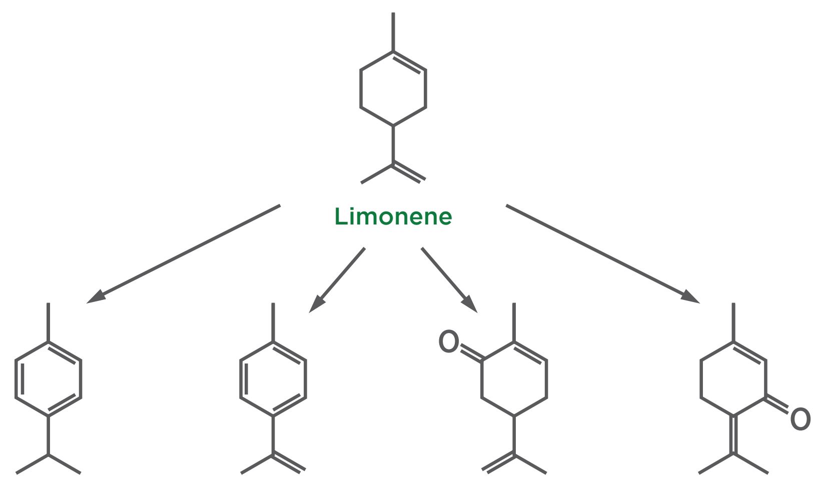
Chemical changes can occur as a result of exposure to heat, light, or oxygen, as well as to the solvents and co-solvents used in extraction and processing. For example, reports indicate that ß-myrcene degrades to hashishene in the presence of light.[6] While a terpene may exert a specific action in its unaltered state, byproducts of its degradation may exhibit wholly different effects. Because cannabis extracts naturally contain so many chemicals—as well as the products of their degradation—it is difficult to determine whether specific changes cause negative or positive effects. Nevertheless, it is possible that these chemical transformations convert a desired ingredient into a deleterious derivative.



ß-Myrcene Hashishene

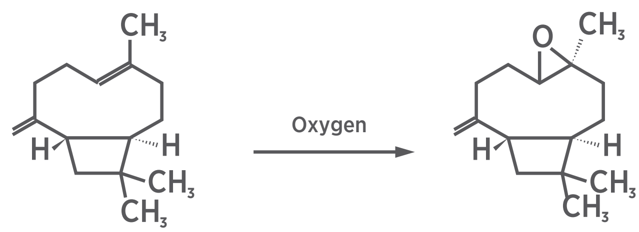
In the same work that evidenced physical changes to terpenes during extraction, Sexton and colleagues also demonstrated that chemical changes can occur. Cannabinoids and sesquiterpenes have similar solubility in supercritical CO_2, so the researchers hypothesized that the cannabinoid content would be greater than the more volatile sesquiterpenes, which might be more easily removed during heating and solvent purge. Contrary to expectation, the group found sesquiterpene concentration to be *higher* after extraction. This indicated that thermal transformation of monoterpenes to other compounds, such as sesquiterpenes, had occurred despite relatively gentle extraction temperatures (49°C maximum).[7]

THERMAL DEGRADATION PRODUCTS OF LIMONENE



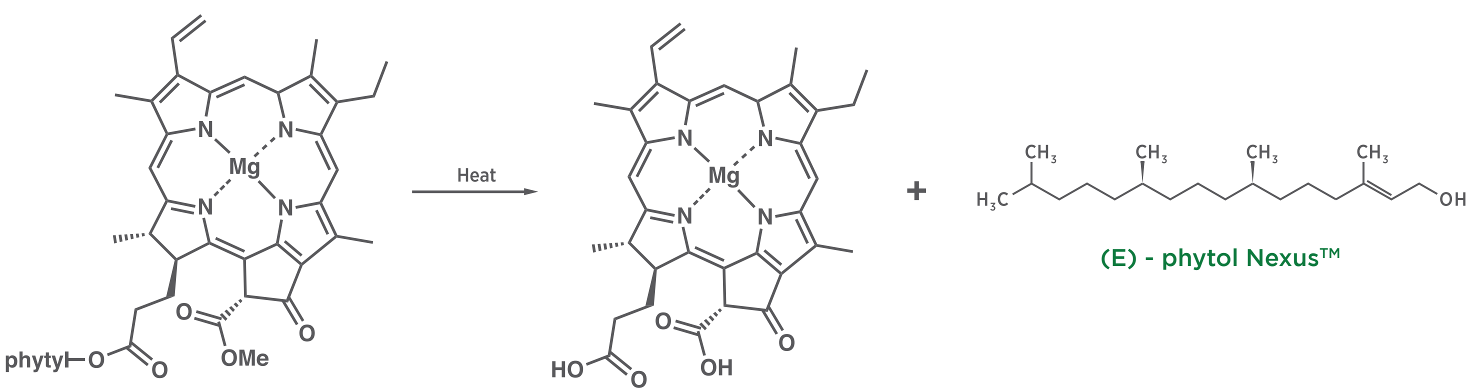
p-Cymene *p*-Cymenene *p*-Carvone Piperitenone

In a different study, Kotra and colleagues investigated the effects of decarboxylation on the chemical composition of resins produced by supercritical fluid extraction (SFE). After SFE under mild conditions, (ambient temperature, with the use of ethanol as co-solvent) a portion of the extract was gently decarboxylated through microwave irradiation (rapid, brief heating to 170°C). Both the CO_2 extraction and decarboxylation processes were designed to minimize the degradative impact of light and oxygen.[8]



ß-Caryophyllene   Caryophyllene Oxide

Despite mild conditions for both process steps, Kotra and coworkers observed significant differences in chemical composition following both SFE and decarboxylation. Following SFE, these researchers found a previously unobserved terpene, caryophyllene oxide, in the produced resin. The presence of caryophyllene oxide, an oxidative byproduct of beta-caryophyllene, demonstrated that cannabis terpenes are altered even under the relatively gentle extraction process employed in this experiment. In addition, the group identified numerous conjugates of cannabinoid acids and terpenoid residues, such as fenchol and borneol. Extraction conditions also caused the hydrolysis of chlorophyll producing phytol prior to the decarboxylation step.



Chlorophyll A

(E) - phytol Nexus™

Following decarboxylation, Kotra and coworkers identified 22 unique compounds in the decarboxylated extract not present in the untreated sample. While some of these twenty-two were the intended neutral cannabinoids, many were the degradative products of terpenes and flavonoids.

Where Sexton and coworkers reported differences in relative terpene ratios between plant and extract by virtue of chemical degradation occurring during extraction, Kotra and colleagues convincingly demonstrated the complete disappearance and appearance of chemical constituents during both extraction and decarboxylation. Taken together, the research of both Kotra's and Sexton's groups demonstrate that chemical changes occur even when using gentle extraction and refinement conditions.

3 STANDARDIZATION, CONSISTENCY & NATURAL

Standardization is responsible for name brand products tasting the same whether you buy them in January or July and in Washington or Tokyo. The same is true for most consumer goods that are composed of natural products such as Scotch whisky, beer, and chocolate. In fact, and often unbeknownst to the end consumer, significant effort goes into maintaining a consistent flavor profile for many commercial products. An organization that extends a brand promise without ensuring consistency can expect customer dissatisfaction and poor brand loyalty, at best.[9]

Products like big-brand orange juice undergo an in-depth process using advanced analytical and blending techniques to ensure a consistent product. Specific blends of natural juices from many different growing regions may be carefully combined with purified components. It is the only way to achieve the predictable taste that consumers expect.[10] The only other option would be to strictly control all environmental variables during cultivation. Not only would that be cost-prohibitive, but it would be a far cry from what most consumers would consider natural.

3A DOES "NATURAL" IMPLY SAFETY?

The use of the word "natural" is controversial for all consumer products. On food labels, the term is not regulated by the U.S. Food and Drug Administration (FDA), which has led to the proliferation of multiple definitions that can differ significantly from its commonly understood meaning. Consumer groups have complained that the term is misleading, because "natural" is often perceived to be synonymous with "organic." These groups find this troubling because a variety of heavily processed ingredients are permissible in supposedly "natural" products.[11] In addition, preservative chemicals without a natural source, ingredients derived from genetically engineered organisms, and high-fructose corn syrup are often found in products carrying the "natural" label.

Recently, the FDA has embarked upon the process of officially defining "natural" as a regulated term.[12] The FDA's current, unofficial working definition of "natural" is:

- ***"that nothing artificial or synthetic (including all color additives regardless of source) has been included in, or has been added to, a food that would not normally be expected to be in that food. However, this policy was not intended to address food production methods, such as the use of pesticides, nor did it explicitly address food processing or manufacturing methods, such as thermal technologies, pasteurization, or irradiation. The FDA also did not consider whether the term "natural" should describe any nutritional or other health benefit."***[13]

With respect to flavor ingredients, the definition of "natural" is even murkier and may vary from one country to another.[14] The definition of a natural flavoring substance even varies significantly between the U.S. and Europe:

- **U.S. Natural Flavor Criteria:** An essential oil, oleoresin, essence or extractive, protein hydrolysate, distillate, or any product of roasting, heating or enzymolysis.
- **European Natural Flavor Criteria:** Source material must be vegetable, animal, or microbiological. Must be produced by a traditional food preparation process.

Under these criteria, a butane-extracted terpene fraction from cannabis would be considered natural in the U.S., but not in Europe. Considering the physical and chemical changes that extraction causes between plant and cannabis extract, the more restrictive European definition seems sensible. Nevertheless, some terpene extracts, such as a steam-distilled fraction, may retain enough fidelity to the plant to warrant a natural categorization.

4 DETERMINING THE SAFETY OF INHALED COMPOUNDS

Determining the safety of compounds intended for inhalation—specifically terpenes—is a difficult process without clear guidelines. Conclusively demonstrating the safety of an additive requires painstakingly assessing the toxicology of each individual component, first in animal models and then in humans. Since separate clinical trials would be required for every compound contained in a flavor blend, this would be prohibitively expensive and time-consuming. Alternatively, safety data from tobacco and inhaled nicotine flavor additives might be used as a proxy for cannabis flavor ingredient safety. Unfortunately, until recently regulators did not require rigorous safety assessments of tobacco additives. Partly because of this, low-dose inhalation of chemicals is not commonly studied and little data is available.

In the absence of satisfactory safety data, one solution would be to assume that inhaling any ingredient found in the cannabis plant would be no less safe than inhaling cannabis smoke or vapor; since inhaling cannabis vapor is considered reasonably safe, consuming its constituents should be, as well. Making such an assumption could obviate the need for testing terpenes found in the plant for safety.

The catalog of ingredients acceptable for use in food products in the United States, the Generally Recognized as Safe (GRAS) for food-use list, began with a similar axiom. Most ingredients initially included in this list were permitted due to the abundance of "experience based on common use in food," as described in 21 CFR 170.30.[16] In practice, components were deemed GRAS if they had a significant history of safe use in food.

Recent academic publications have provided sufficient analytical data to assemble an analogous inventory of native cannabis ingredients. This compilation could form the basis for a white list of compounds expected to be reasonably safe for addition to cannabis products and incorporated into cannabis regulatory frameworks. As the data presented above detail, simply using ingredients that have been derived from cannabis itself is not a satisfactory proxy for safety because constituents degrade and new compounds can be generated during extraction. Such changes alone suggest that further ingredient standards are necessary. Part of that may involve a closer look at the composition of ingredients extracted from cannabis to ensure that they have not been materially changed.

For terpene and flavor blends—whether crafted from purified feedstocks or from the cannabis plant—solvent residues can be a persistent contaminant. Much like some forms of cannabis-derived terpenes, most commercially available terpenes and esters are isolated via solvent extraction. Similar to high-quality shatter, there are techniques to reduce solvent residues, but these are often time-consuming and expensive. As such, cheaper products may contain higher levels of residual solvents, greater concentrations of industrial chemicals (e.g. benzene) or unwanted preservatives (e.g. BHT). Whether you are a manufacturer that would like to avoid failing a residual solvent test on your finished concentrate, or a consumer that wants a clean cannabis product, it is imperative that you know your sources and their standards.

In a separate whitepaper, we propose a system of cannabis flavor ingredient standards based upon a native cannabis compound inventory and other simple regulatory principles. It is clear that the unique patterns of use and physiological effects of cannabis (cf. Ensemble Effects) demand separate standards for cannabis ingredient safety, supported by research

DID YOU KNOW?

The Hebrew word "kosher" translates to mean right or proper. It is a common misconception that a blessing from a rabbi is all that is required to make a food product or ingredient kosher. In fact, it is necessary to determine whether any components or ingredients have been derived from animals. This can prove difficult as many flavor components are produced via fermentation, which often utilizes beef extract or peptones.[15]

5 PRACTICAL RECOMMENDATIONS & SUMMARY

This research should remind all cannabis consumers that just because a product comes from a plant, does not guarantee its similarity to that plant. Furthermore, a product labeled "natural" may not meet the common definition of that word as safe, organic or unaltered. When comparing a plant to its concentrate, always ask for analytical data on both. When analytical data is unavailable, it can be effective to simply trust your nose and palate: If your cannabis product does not smell and taste like the plant it comes from, chances are that the effects will also be different.

CERTIFIED CANNABACEUTICALS®
Certificate of Analysis

KONA GOLD FLOWER

Client:	TWS	Tested On:	4/17/2018
Sample:	Kona Gold Flower	Type:	
Sample ID #:		Unit Mass:	N/A
Lot ID #:		Unit of Measure:	

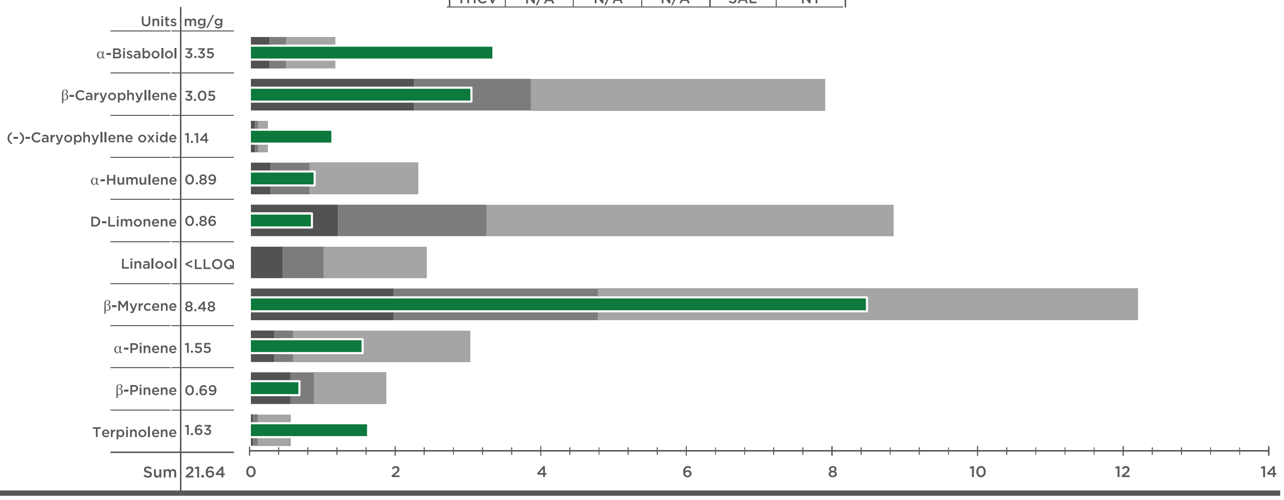
Cannabinoids[1]	Max[3]	Neutral	Acid
THC	17.81	0.73	19.49
CBD	0.21	0.29	0.04
CBG	0.98	0.08	1.03
CBC	N/A	0.01	N/A
CBN	N/A	0.01	N/A
THCV	N/A	N/A	N/A

Microbiology[2] Test	Result
BTGN	NT
TAC	NT
Y&M	NT
TCOL	NT
ECOL	NT
SAL	NT

Inspection	
% Moisture:	NT
% Stems:	NT
% Other:	NT

Residual Solvent Type	ppm
NT	N/A
NT	N/A

TERPENE ANALYSIS



KONA GOLD CONCENTRATE

Client:	TWS	Tested On:	4/17/2018
Sample:	Kona Gold Concentrate	Type:	
Sample ID #:		Unit Mass:	N/A
Lot ID #:		Unit of Measure:	

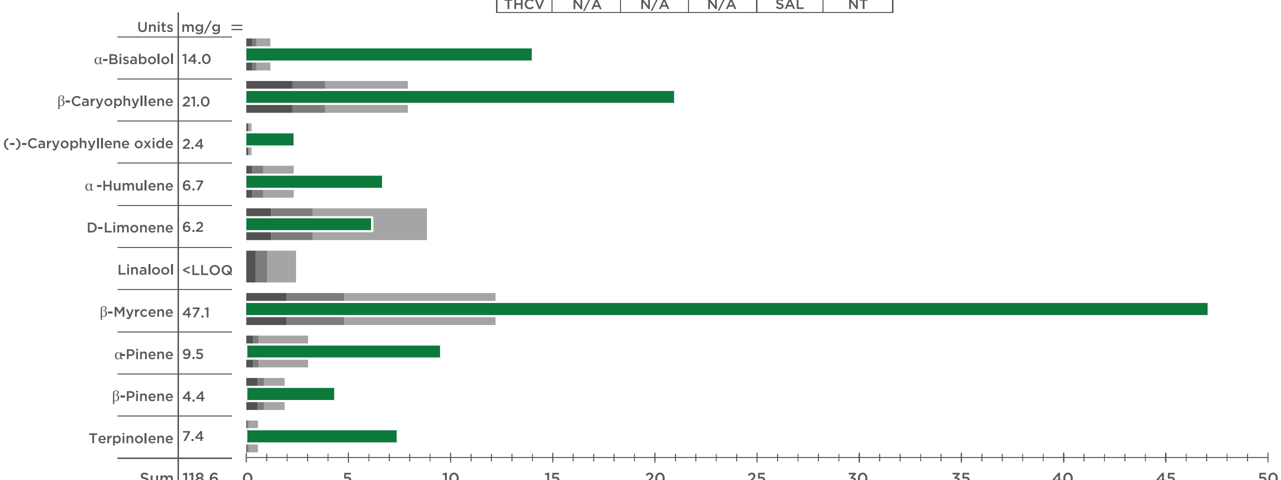
Cannabinoids[1]	Max[3]	Neutral	Acid
THC	75.26	75.26	ND
CBD	0.42	0.42	ND
CBG	3.51	3.51	ND
CBC	N/A	1.40	N/A
CBN	N/A	0.80	N/A
THCV	N/A	N/A	N/A

Microbiology[2] Test	Result
BTGN	NT
TAC	NT
Y&M	NT
TCOL	NT
ECOL	NT
SAL	NT

Inspection	
% Moisture:	NT
% Stems:	NT
% Other:	NT

Residual Solvent Type	ppm
NT	N/A
NT	N/A

TERPENE ANALYSIS



[1]Cannabis samples can show considerable intra- and inter-plant variability. The test results presented above are accurate only for the sample analyzed. Depending on sampling protocols followed by the sample creator/collector these results may not be representative of the entire product lot/batch.

[2]Standards for CFU levels established in compliance with WA I-502 for each product class.

[3]Maximum cannabinoid concentration is calculated with: Max. = Neutral + 0.877 x Acid.

*All proprietary marks and branding registered in trade appropriate jurisdictions globally

Dried Flower Reference Levels

Low	Medium	High

Acronym	Meaning
< LLOQ	Below lower limit of quantification
N/A	Not applicable
ND	Not detected
NT	Not tested

Microbiology Test Legend

Code	Test	CFU Limit
BTGN	Bile-tolerant gram negative	< 1,000
ECOL	Escherichia coli	Absent
SAL	Salmonella	Absent
TAC	Total aerobic count	< 100,000
TCOL	Total coliforms	< 1,000
Y&M	Total yeast & mold	< 10,000

TERPENE MYTHS & FACTS			
CANNABIS-DERIVED TERPENES ARE		**TERPENE FORMULATIONS NOT DERIVED FROM CANNABIS ARE**	
✗	Superior because they are natural	✗	Fake
✗	Identical to that in the plant	✓	Often natural
✓	Prone to geographic and seasonal variation	✗	Identical to that in the plant
?	Free from THC, allowing for legal shipping	✓	Typically more consistent

Since, terpenes can change significantly on exposure to oxygen and high heat, vaping tends to retain the integrity of the terpene composition better than smoking. Combustion, caused by the application of flame to the plant material, can destroy those terpenes. Whether using a vape pen or a dab rig, lower temperatures can better preserve terpenes. More heat will cause terpenes to degrade or even flash vaporize and escape the pull of your lungs. Turning the voltage dial down on a vaporizer pen or only heating nails to intermediate temperatures can help prevent this degradation. An optimal temperature is just hot enough to vaporize cannabinoids and no higher.

A key takeaway from this whitepaper is that source matters when it comes to terpenes. How terpenes and other flavor constituents are produced and what measures are taken to ensure quality is more important than the provenance of the ingredients themselves. Whether extracted from cannabis or crafted from other sources, the terpene and flavor fractions used in your favorite product demand discipline and standards.

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