Terpenes are being added to numerous cannabis products to enhance flavor and boost potential health benefits.

NATURAL PRODUCTS

Cannabis industry gets crafty with terpenes

Latest craze goes beyond scents, flavors to potential health benefits

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Terpenes, terpenoids, terps. Whatever you call them, these compounds in cannabis that give it distinctive aromas and flavors are popping up in consumer products everywhere. In US states where medical and recreational cannabis is legal, companies are spiking tinctures, vaping oils, lotions, foods, and beverages with terpenes, along with cannabinoids like tetrahydrocannabinol (THC) and cannabidiol (CBD). In other places, companies are marketing similar products minus the THC, with labels claiming "whole plant" medicine or "full spectrum" CBD.

The idea is that terpenes enhance the health benefits of the products either alone or synergistically with other terpenes, THC, CBD, and other minor cannabinoids found in cannabis. Most research has focused on the health effects of individual terpenes. For example, linalool, a terpene also found in lavender, provides antianxiety effects. α-Pinene, which is also produced in rosemary, can be invigorating and lead to mental alertness. Much less is known about how terpenes work together and in combination with cannabinoids.

"We have barely begun to understand the therapeutic potential of cannabis," says Ethan Russo, a neurologist and director of R&D at the International Cannabis and Cannabinoids Institute, based in the Czech Republic. "We haven't taken the steps that are required to really harness the abilities of some of these minor cannabinoids, particularly in conjunction with optimized terpenoid profiles."

Russo prefers the term *terpenoid* over *terpenes* because "terpenes are hydrocarbons. Terpenoids may have oxygen or other elements, so *terpenoid* is actually the more encompassing term," he says. "But when people are speaking cannabis, they are pretty much synonymous."

A nebulous understanding of how terpenes interact with other chemicals in cannabis, however, isn't stopping cannabis companies from jumping into terpenes. Manufacturers are getting creative and adding the flavorful compounds to a wide array of products to try to mimic—or enhance—terpene profiles found in cannabis flowers.

Plants create terpenes to protect themselves from predators or to lure pollinators. Each different strain or chemical variety of cannabis, sometimes called a chemovar, has its own signature of terpenes and cannabinoids. There are hundreds, if not thousands, of these chemovars, each with random-sounding names that often allude to the kind of sensory experience a user may feel. For example, Lemon Kush is high in limonene, a terpene also found in citrus peels that is known for its mood-elevating and antibacterial properties. Blue Dream is high in myrcene, known for its relaxing and sedative effects. Sour Diesel is high in both myrcene and limonene, a combination known for its energizing and stress-relieving effects.

Just because two varieties of cannabis are sold under the same name, however, doesn't mean they have the same chemical profile. Most of the time they do not.

A huge number of variables affect the terpene profile of plants, says Amber Wise, scientific director at Medicine Creek Analytics, a cannabis-testing lab in Washington State. If plants with the same ge-

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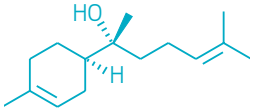
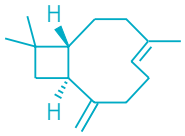
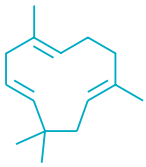
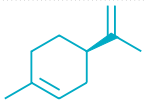
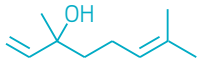
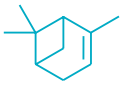
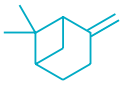
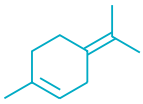
Terpene therapeutics

The strong-smelling chemicals in cannabis products may be beneficial to your health—and they may also come from other sources.

TERPENE	STRUCTURE	ALSO FOUND IN	AROMAS AND FLAVORS	HEALTH EFFECTS
α-Bisabolol			Coconut, fruity, nutty	Antibacterial, anti-inflammatory
β-Caryophyllene			Clove, dry, spicy, woody	Antimicrobial, anti-inflammatory, neuroprotective
α-Humulene			Bitter, floral, peppery, woody	Antibacterial, anti-inflammatory
(+)-Limonene			Citrusy, sweet	Antibacterial, mood elevation, stress relief
Linalool			Floral, rose, woody	Antianxiety, sedative
Myrcene			Celery-like, herbaceous, turpentine-like, woody	Analgesic, sedative, relaxing
α-Pinene			Cool, fresh, herbal, piney, turpentine-like	Alertness, possible memory retention
β-Pinene			Green hay, piney, spicy, woody	Anti-inflammatory, bronchodilator
Terpinolene			Fresh, lemon peel, sweet	Antibacterial, antifungal, possible sedative

Source: The Werc Shop. **Note:** Health effects have largely been studied for individual chemicals in isolation, not in mixtures.

netic makeup are grown outdoors versus indoors, "you can end up with different terpene profiles at the end because temperature, growing medium, nutrients, sunlight, all kinds of things affect the terpene profile of plants," Wise says.

David Heldreth, a longtime cannabis grower and medical-cannabis patient, began nearly a decade ago to investigate how various growing conditions affect the composition of cannabis. He patented a series of lighting changes and fertilizer, plant growth hormone, and enzyme treatments that increase the production of minor cannabinoids, such as cannabigerol and cannabichromene, as well as specific terpenes.

Today, Heldreth is the chief science officer at True Terpenes, an Oregon-based company that markets terpenes to companies that reformulate them into various consumer goods. Companies are adding True Terpenes' formulations to edibles such as chocolate, beverages such as soda and beer, and various skin lotions, Heldreth says. Manufacturers are also adding such terpene formulations to vaping oils that contain cannabinoids.

Demand for terpenes is booming in the US now that CBD from hemp is legal across the country. It is currently too expensive to harvest and extract CBD from hemp flowers, so companies are using the entire plant, including the leaves and stalks, Heldreth says.

Many companies use ethanol to extract CBD from the whole plant material. When the ethanol is removed, terpenes are lost through volatilization. So companies often reintroduce terpenes into their final products. Unfortunately, "there aren't any extra terpenes around from cannabis," Heldreth says.

True Terpenes sources its terpenes from other natural products, such as getting linalool from lavender and limonene from citrus. The company works with cannabis growers to obtain analytical data on terpenes in various cannabis strains. It then develops formulations that contain about 40 terpenes at percentages that mimic the chemical signatures of popular cannabis strains. The formulations are mixtures of essential oils, which are generally recognized as safe by food regulators, in a suspension of refined coconut oil.

Cannabinoids are not water soluble,

and formulation strategies differ for edible and topical products compared with those intended for inhalation. In aqueous products like beverages, cannabinoids are often encapsulated in micelles and microemulsions using proprietary methods developed by pharmaceutical companies.

Vaping oils require a thinning agent, such as propylene glycol, poly(ethylene glycol), or vegetable glycerin—the same chemicals used in e-cigarette liquids. Some companies, like True Terpenes, use medium-chain triglycerides from refined coconut oil.

When these thinning agents are heated, they emit formaldehyde, warns Jeff Raber, cofounder and CEO of the Werc Shop, a California-based cannabis contract manufacturing and testing firm. It is not something you want to inhale, he says.

The Werc Shop was granted a US patent earlier this year related to a thinning agent made up of the terpene phytol and related compounds. The company now markets a formulation called Nexus 2.0 that combines phytol with other terpenes and compounds found in cannabis. The formulation improves the stability, performance, and inhalation safety of vaping products, Raber claims.

The Nexus formulation also aims to offer the same taste and effect that plant material does. "Our terpene formulations can comprise more than 50 components," Raber says. "They are what we call 'true to plant.'"

The concentration of terpenes in vaping oil typically ranges from 5 to 15%, depending on the preferred end formulation, Raber says. If the concentration is too high, "it can actually sting your lips or tongue," he says. "It can taste bad if not done well."

> "We don't know anything about vaping terpenes or the degradation products that they might form after high heat exposure."
>
> **—Amber Wise,** scientific director, Medicine Creek Analytics

Some people can also develop allergies, such as skin and inhalation sensitivities, to terpenes. Many of the allergens in fragrances are terpenes, says Julie Kowalski, chief scientific officer at Trace Analytics, a cannabis-testing lab in Washington State. People need to think about allergies, particularly "when they are formulating products where they put in artificially high amounts of terpenes," she says.

Most companies aim to replicate the terpenes in cannabis flowers at ratios that occur naturally. But not all manufacturers are doing it well.

"We've seen concentrations of up to 20% terpenes in some formulations," Wise says. Such high levels of terpenes are "terrifying from a public health standpoint," she says. Terpenes are typically found in cannabis flowers at levels of 2–5%.

"We don't know anything about vaping terpenes or the degradation products that they might form after high heat exposure," Wise says. Terpenes are highly reactive molecules that isomerize and interact with O_2, she notes. But "it is a big unknown as to what happens when you heat them up, smoke them, or vape them," she says. Variability of vape-oil composition makes it particularly challenging to study terpenes' health effects.

Olala, a recreational-cannabis company in Washington, started out making vape oils. Today, the company's biggest source of revenue is cannabis beverages—sodas, coffee, sparkling water, and terpene tonics—says the firm's president, Randy Reed.

The company focuses on being a "best-in-class-type manufacturer, whether it be making beverages, vape oils, topicals, or capsules," Reed says. "We don't know what direction the cannabis industry is going. You've got to be flexible." To that end, Olala has developed a manufacturing facility that can pivot quickly and change to give consumers the products they want, Reed says. That includes making products with specific terpene profiles, as well as THC and other cannabinoids.

Olala products start with fresh cannabis flowers. The company extracts all the cannabinoids and terpenes it can using a multiphase carbon dioxide extraction technique with ethanol modifiers. The method involves using subcritical CO_2 to fractionate off the terpenes, followed by supercritical CO_2 to pull out cannabinoids.

Each fraction is characterized and quantified, so the company has full control over how much of each ingredient is added back into its products. "For our edibles, we don't want all those terpenes in there," Reed says. The smell and taste of the terpenes, which can be quite bitter, would overpower whatever other flavor is in the product—for example, orange cream or lemon lime in a soda—he says.

Other Olala products, such as vape oils and terpene tonics, which are formulated to taste like specific cannabis flowers, have higher terpene concentrations. According to anecdotal evidence, terpene tonics that are high in myrcene or linalool will make you feel more relaxed, Reed says. Other terpene tonics that are high in α-pinene and terpinolene will give you a more uplifting effect, he adds. The terpene tonics are "kind of a craft maker thing," Reed says. "You have a feel for the various chemovars or the chemical profiles of the flower."

Olala's inclusion of THC in its products differentiates it from much of the CBD industry, which markets products for wellness rather than recreation. So-called full-spectrum or whole-plant CBD tinctures without THC are increasingly popular. These extracts contain several minor cannabinoids in addition to CBD. The problem is there are "reportedly over 300 online CBD hemp

companies," says Bonni Goldstein, medical director of Canna-Centers, a California-based medical cannabis practice. There is no way to tell what is in those bottles other than to ask the company for a certificate of analysis or pay for a lab to test a sample, she says. There are good-quality CBD products and "garbage," she warns.

Goldstein treats children with epilepsy, cancer, severe attention deficit hyperactivity disorder, debilitating Tourette's syndrome, and mental health disorders like anxiety, depression, and self-injury. She emphasizes the importance of accurate labeling on CBD oils when they are used for medical purposes.

Last year, the US Food and Drug Administration approved the first pure CBD drug, Epidiolex, for treating seizures in children with two rare disorders. The drug, manufactured by GW Pharmaceuticals, does not contain any other cannabinoids or terpenes derived from cannabis.

Epidiolex gives certainty in CBD dosing, but researchers in Brazil have found that it is less effective than equivalent doses of CBD in extracts that also contain the full array of cannabinoids and terpenes found in cannabis flowers. They reported that it takes a lot less, about 22% of the dose of pure CBD, to treat severe seizures with whole-plant CBD extracts (*Front Neurol.* 2018, DOI: 10.3389/fneur.2018.00759).

"Because of the synergy, even a touch of THC or anticonvulsant terpenoids such as linalool can make a difference between control and lack of it" with respect to seizures, the International Cannabis and Cannabinoids Institute's Russo says. "If you need five times as much of the pure-compound CBD, it doesn't mean that CBD is bad medicine. It means that the plant does it better."

Whole-plant extracts not only are more effective but also have fewer side effects than pure CBD at higher doses, Russo says. The bottom line, he says, is that "whole-cannabis extracts are going to have an advantage over pure compounds in almost every instance."

Consequently, some parents of children with chronic conditions continue to use CBD oils rather than Epidiolex. Such oils may be whole-plant extracts or they may be CBD extracts with terpenes added. People who buy CBD oils online sometimes pay for the oils to be tested by private laboratories, Goldstein says. In some cases, labs reported high levels of pesticides, lead, and isopropyl alcohol, she says. In other cases, the amount of CBD in the bottle was too low for treating a pediatric patient with epilepsy.

These problems drive many families to make their own oils by purchasing raw cannabis flowers from a dispensary, Goldstein says. Doing so allows them to control the quality as well as to try numerous varieties that are not available as prefabricated manufactured oil, she notes. Each variety has subtly different effects, and some work better than others for particular patients.

Using oils or extracts from cannabis flowers directly is the best way to achieve health benefits from cannabis, some argue. "There is a purist argument that you should keep cannabis together" and not introduce terpenes from other natural products, says Toby Astill, global food market manager at the instrumentation company PerkinElmer. But it probably doesn't matter where the terpenes come from, assuming they are of food-grade quality and product manufacturers can match the profiles found in cannabis flowers. "At the end of the day, if you analytically know what your terpene is, it is the same chemistry from either source," he says. "It does work both ways." ■