Treatment With Cannabis and Cannabinoids: Some Practical Aspects and Controversies

By Ethan Russo, MD

Ethan Russo, MD, resigned as senior medical advisor at GW Pharmaceuticals at the end of 2014. During his decade with the company, Russo was somewhat constrained in his public comments about cannabis use, research, and politics. Steph Sherer of Americans for Safe Access invited him to speak his mind at ASA's 2015 conference, which was held in Washington, DC, in late March. This article is based on his talk.

To talk about some of the confusion surrounding cannabis, first we have to introduce the endocannabinoid system —an internal homeostatic regulatory system that is involved in almost every physiological process. It has three components: the receptors CB1 and CB2, their biosynthetic and degradative enzymes, and the endocannabinoids themselves – anandamide and 2AG. There are active and inactive components that work in concert to achieve what Dr. Raphael Mechoulam has described as "the entourage effect."

There are cannabinoid receptors throughout the body. CB1 is the most abundant G-protein-coupled receptor in the central nervous system, with a major neuromodulatory function. It is found in the periphery as well. Its role has been characterized by Vincenzo DiMarzo as "relax, eat, sleep, forget and protect." CB2 is an immunomodulatory receptor found mainly in the periphery. It plays an important role in pain and inflammation.

This slide *(bottom left)* illustrates the biosynthetic pathways of cannabinoids in the plant. These are produced as carboxylic acids that are then customarily decarboxylated by heat to produce the familiar pentyl cannabinoids (with five-carbon side chains), tetrahydrocannabinol (THC), cannabidiol (CBD) *et al*.

Cannabis is also capable of producing propyl cannabinoids with three-carbon side chains, depending on the enzymes available. *(Slide at bottom right.)* Professor Mechoulam has called this an example of "Nature's Law of Stinginess," but I call it "enzymatic-substrate promiscuity," or ESP. Cannabis has ESP.

Below is a breakdown of cannabinoid content in a pharmaceutical plant analyzed by David Potter. Note that cannabinoids are not present at all in the roots or seeds (which both contain other beneficial compounds).

Seeds 0%
Roots 0%
Stem 0.3%
Leaves 0.8%
Seeded female buds 6.3%
Unseeded female buds 15.2%

Cannabinoid distribution in a pharmaceutical plant is highly concentrated in unseeded female flowers (also known as ganja, sinsemilla and other terms of endearment).

One thing that is *not* misunderstood: the unfertilized female flower is the most important medicinal portion of the plant. "Sinsemilla" buds contain 18 times the amount of THC and other cannabinoids present on the leaves.

There are many people who juice leaves and report medical benefit. If this benefit derives from cannabinoids,

Trichomes are glands that produce cannabinoids and terpenoids. Sessile trichome (above) is much flatter and smaller (20 microns in diameter) than the capitate trichome at right (100 microns). Sessile trichomes sit directly on leaves. Capitate trichomes are globular and sit on stalks that keep their acidic contents away from the flowers. Juicing leaves is an inefficient way to ingest cannabinoids. Photos by David Potter

whether raw or decarboxylated, it's from a very small amount.

The true production facility for cannabinoids in the plant are the glandular trichomes. There are two main kinds: capitate trichomes, are found on the flowers. They are globular and sit on stalks that keep them away from the flowers. Sessile trichomes are flatter and sit directly on the leaves.

Applying the formula for the volume of a sphere, we see that there's about 100 times more volume in the capitate glandular trichomes.

Additionally, the biochemistry is different. In the leaves there are a lot of bitter sessile terpenoids that are there to prevent grazing by deer and other animals that will try to eat the plant. This may be why people occasionally get sick from juicing leaves of cannabis.

It is true certain cannabis plants that have cannabidiol in them will be sedating, but it's not because of the cannabidiol. It's because those plants tend to be myrcene-dominant.

Cannabidiol —CBD— is a molecule that some of us have been trying to call attention to for 20 years. The structure was elucidated by Professor Mechoulam in 1963, a year earlier than THC. But it got lost in the shuffle because it doesn't have the sexiness of being psychoactive.

One myth is that a little bit of CBD will have a significant impact and counter the effects of THC. In general, to get a real medicinal effect, there has to be a substantial amount of CBD.

The best ratios are probably 1:1, which is akin to what we'd see in a plant in Afghanistan and Morocco in the olden days, before selective breeding changed it to be all about THC.

There is a persistent myth that cannabidiol is sedating.

What CBD does do with regular usage is increase the amount of anandamide, the best-known endogenous cannabinoid in the body.

It is not. It has been clearly shown with EEGs and other methods that CBD is a very stimulating molecule at low and moderate doses.

Sedation may occur at very high doses, particularly in association with the smorgasbord of pharmacological agents that kids get put on, there can be drug-drug interactions that produce sedation. But in general, CBD is not a sedative.

It is true certain cannabis plants that have cannabidiol in them will be sedating, but it's not because of the cannabidiol. It's because those plants tend to be myrcene-dominant. Myrcene is a terpenoid with sedating, narcotic-type properties. In combination with THC, myrcene is responsible for couch lock.

There also is a prevalent myth that CBD turns into THC in the body. This is based on outdated research. It was once thought that the biosynthetic pathway to THC went through CBD. That is not true. When pure CBD has been ingested and pharmacokinetics are done to look at what's in the blood afterwards, no THC has been produced.

There is also a myth involving THCA. The plant does not produce THC acid to get people high once it's been dried and decarboxylated. It's there because it's insecticidal. Additionally, THCA has been shown to be a very strong anti-inflammatory without being altered to THC. .It also affects tumor necrosis factor alpha, which plays a role in a number of diseases.

Many families have added THCA to their child's regimen to treat seizures. We have to analyze why it provides benefit. Back in 1978 the anti-convulsive properties of THCA were tested by Karler and Turkanis, and it was found that a very high dose was required to produce an effect —up to 400 milligrams per kilogram of body weight per day, whereas CBD requires 100mg/kg.

If somebody used leaves to get THCA, they'd need about 2,200 leaves a day to get the anticonvulsant dose. Clearly, if THCA is needed, it should come from the flower and not from the leaves, which make good compost or could be used otherwise.

CBDA —cannabidiol acid— which is present in fresh hemp, is a natural pesticide. It was noted hundreds of years ago when hemp was being retted in ponds, it killed the fish.

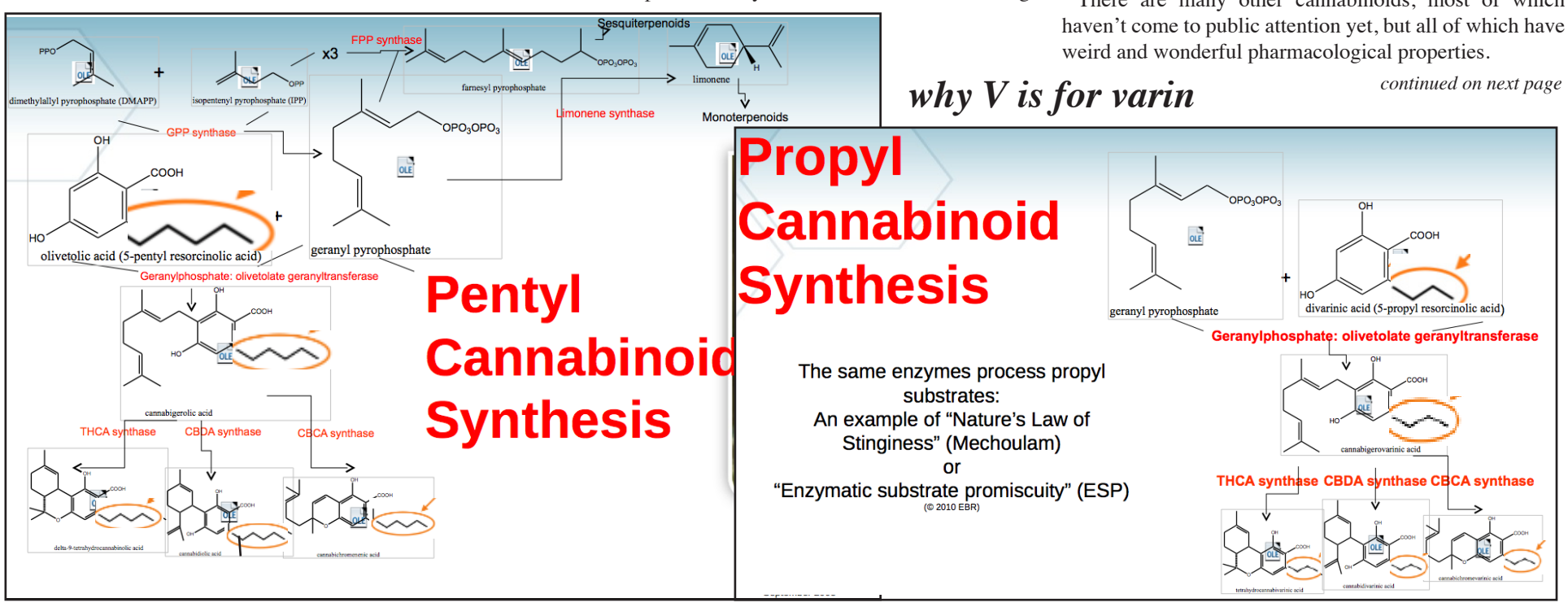
It has also been shown that CBDA prevents vomiting. It is a very powerful anti-emetic —much more powerful than CBD or THC. It works through stimulation of the Serotonin 5-HT1A receptor, which is one of the main mechanisms involved in other beneficial effects.

CBDA also has a strong effect on tumors, but this use is really not new. It was described by Renaissance herbalists quite extensively. It's only now that we have the chance to study CBDA in a lab.

There are many other cannabinoids, most of which haven't come to public attention yet, but all of which have weird and wonderful pharmacological properties.

continued on next page

why V is for varin



The *Cannabis* plant synthesizes THC acid and CBD acid by combining geranyl phosphate with olivetolic acid (which has a five-carbon 'tail' that gets retained in the process). Cannabis employs the same enzymes —THCA synthase and CBDA synthase— when combining geranyl phosphate and di*varin*ic acid (which has a three-carbon tail that similarly gets retained) to synthesize THCV and CBDV. Thus THC and CBD each have a five-carbon pentyl group attached where CBDV and THCV each have a three-carbon propyl group in their tails, and *varin* in their names. The varinic acid form of cannabichrome (CBCVA) is the third propyl cannabinoid in these graphics from Russo's power point.

Russo's Keynote *from previous page*

What misleads people about the importance of terpenoids is that they're present in very tiny concentrations in the plant.

Some of us have been trying to convince people for a long time that the terpenoids in Cannabis are important. Many are analgesic and anti-inflammatory in their own right. And many have psychoactive properties. What misleads people about their importance is that they're present in very tiny concentrations in the plant. But they're extremely potent molecules, and in combination with the cannabinoids they make a big difference in a plant's medicinal properties.

The species controversy. You'll hear a lot about sativas and indicas, most of which is nonsense, because even the taxonomists can't agree. Taxonomists are the people who define what species is what in botany—and they are constantly changing their minds. There's no uniformity of opinion at all. They're worse than neurologists.

The prevailing notion is that Cannabis is one species with varieties. *(See John McPartland's take on page 17.)* Ernest Small in Canada has identified three basic types. Type 1 is a high-THC plant. Type 2 is mixed THC and CBD, the way cannabis frequently was in the past. And Type 3 is CBD predominant.

Some years ago, Karl Hillig did a series of articles showing that what really distinguished one *Cannabis* variety from another was their terpenoid content. This has been demonstrated subsequently by Jeffrey Raber in his survey of plants grown in California.

Very rarely do cannabis dispensaries provide medical consumers with relevant information about their products. What's its specific cannabinoid content? What's its specific terpenoid content? How does it taste when vaporized? And how should it be used? What conditions is it good for? What have patients reported in terms of benefits? What might be in there that shouldn't be in there?

A format developed by Mark Lewis and Matt Giese of Napro Research provides a great deal of useful information (*See illustration at bottom of page.)*

A brief comment on Marinol, which I find problematic. Synthetic THC was approved as a medicine, dronabinol, in 1985; Marinol is the trade name. When it was down-scheduled from Schedule 1 to Schedule 3 in 1999, I used it extensively in my practice. Over the course of four years, I found that even people who are accustomed to cannabis had trouble with Marinol. It's very quirky. It tends to produce dysphoria rather than euphoria. The dose is often too high. People are fine and they're suddenly too high. It's very expensive. And it lacks all those accoutrements, the synergistic components of whole cannabis.

Typically, about 15 percent of the THC is actually drawn into the lungs.

Smoking cannabis —the most common method of application— is problematic. It remains illegal in most jurisdictions, and even where it's legal, you're not supposed to do it publicly. Smoking is very wasteful of THC. Typically, about 15 percent of the THC is actually drawn into the lungs.

Contrary to the wishes of many people, smoked cannabis just cannot get through the FDA approval process.

Although smoking cannabis alone, without tobacco, has not been linked to the development of lung cancer, it does produce polyaromatic hydrocarbons, which are carcinogens. The body has to process them, which puts an unnecessary metabolic demand on the liver. Irritants in the smoke cause bronchitis.

Vape pen heating element (left) turns red-hot in seconds. "This is burning, not vaporizing," said Russo. Vape pens using propylene glycol as a propellant have been shown to produce cancer-causing formaldehyde. Photos by Ethan Russo

As much as we'd like to demarcate ourselves from insects, if a substance kills an insect, there's a good chance that it's not good for you, either.

There is also the real danger of inhaling toxic pesticide residues when cannabis is smoked. Jeff Raber and colleagues at the Werc Shop, a lab in California, applied pesticides —Diazinon, Paclobutrazol, Bifenthrin, Permethrin— to cannabis and then measured how much came through when the material was "smoked" by bong (with and without filters) and glass pipe. The result was an ominous 40 to 70 percent.

I queried labs in California and was told that between 15 and 35 percent of their samples from growers and dispensaries had pesticide residues.

Abamectin and other pesticides that are cholisterase-inhibitors, if present in cannabis used by someone with epilepsy, can induce seizures. Even someone who doesn't have seizure tendency can have a seizure if they're exposed to neurotoxic pesticides in sufficient amounts. As much as we'd like to demarcate ourselves from insects, if a substance kills an insect, there's a good chance that it's not good for you, either

Vaporization is preferable to smoking as a delivery system for cannabis, but it's not perfect. The idea is to vaporize cannabinoids and terpenoids at a lower temperature that does not burn the material to produce smoke. Unfortunately, there has not been a study to date with the Volcano —a very good machine— or any other vaporizer that showed a total absence of polyaromatic hydrocarbons. Again, we can't say that they will cause cancer if somebody's not smoking tobacco. But we can say that the FDA is never going to approve a device that produces any amount of these.

Arno Hazekamp did a survey of consumer preferences in the Netherlands in 2013 and reported that only 27% of medical users were vaporizing. Smoking still predominated, which is really suboptimal in terms of harm reduction.

Edibles are reportedly gaining popularity, and consumers are being offered extracts in a variety of formats. But the industry has serious quality control problems. The American Herbal Pharmacopeia and other organizations are trying to develop standards that I think will be a boon to consumers, whether recreational or medicinal.

Confections, particularly ones packaged to look like real candy with catchy names, are attractive to children, and you can understand that the DEA would look askance at this kind of thing.

Particularly for patients with chronic conditions, oral administration could be a big advantage because it doesn't require frequent dosing throughout the day. With modern hash-making techniques and a good chemovar, it's possible to get the THC level of a concentrate up to about 60 percent. I would seriously question why people need any more than that. How high does a patient need to be to have symptom relief?

Recreationally, people will take what they want to take, but for the medical user, what's important is proper administration with maximum harm reduction.

"Dosing is a crucial issue therapeutically. Dosing should be to the point of symptom relief rather than psychoactivity. Two point five milligrams of THC is a threshold dose for most patients. Five milligrams is usually effective and tolerated. Ten milligrams is too much for many people, but not for those with tolerance.

But the quest for higher levels of THC continues, and "dabs" keep gaining popularity.

Cannabinoids and terpenoids are sticky substances. Polar solvents —either a fat or alcohol— are required to extract them. But many of those same solvents are flammable or explosive. Not a week goes by in this country that somebody doesn't blow themselves up trying to do a butane extraction at home. Butane and naphthalene can leave toxic residues. Not just cannabinoids but contaminants, too, are highly concentrated by the process.

It just mystifies me how people can be environmentalist vegans, so fastidious in their habits otherwise, and yet accept this kind of solvent in the material that they're inhaling. People who use dabs acknowledge that they suffer onset of tolerance and even withdrawal symptoms when they refrain. So, I don't think that dabs are ideal at all for medical users.

Again, I would ask the question, how high does a patient really need to be to get relief? Development of tolerance should be avoided. There is a sweet spot in therapeutics that is achievable and desirable where symptoms are treated without intoxication.

Just a little more about wax. We now have these devices called "vape pens," which are a misnomer in most instances. An unheated heating element *(photo at left, above)* will turn red hot with seconds of the device being turned on *(photo at right)*. I guarantee you this temperature is way above the vaporization point of THC and terpenoids.

text continued on bottom page 24

Ethan Russo, MD, addressing the Americans for Safe Access "Unity Conference" in Washington, DC, March 2015. When asked if O'S could run a print version of his talk, Russo expressed concern about being perceived as "a scold." Russo is not a scold, he's a doctor — a neurologist. He's also an ethnobotanist, a novelist, a historian, an educator, and a Grateful Dead fan.

With John McPartland in 2001, Russo challenged the medical establishment's assumption that single-molecule, "silver bullet" medicines are superior to herbal medicines with their "shotgun" full of active compounds.

It was Russo who first proposed that a "Clinical Endocannabinoid Deficiency" was associated with various ailments. His 2004 paper in Neuroendocrinology Letters asked "Can this concept explain therapeutic benefits of Cannabis in Migraine, Fibromyalgia, Irritable Bowel Syndrome and other Treatment-Resistant Conditions?"

Over the years no one has done more than Russo (and McPartland, David Watson and Rob Clarke) to publicize the role of terpenoids in determining the effects of cannabis.

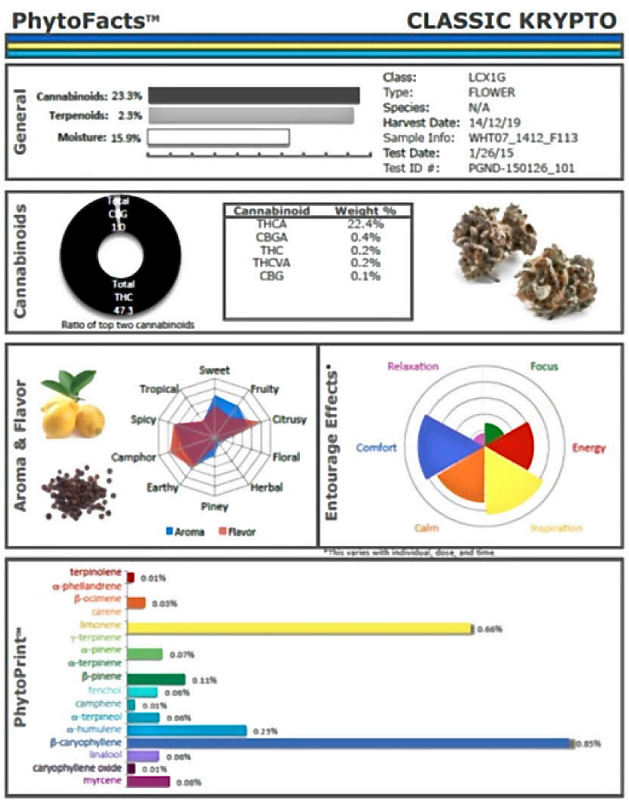
Useful Info

Russo praised the format devised by Mark Lewis and Matt Giese of Napro Research to provide "the information that a consumer would really need in helping to select a strain to use for their condition: cannabinoid content and terpenoid content, a picture of the actual plant, what the notes are in terms of its scent and taste, the effects that people get from it..."

With reference to a slide *(graphic at right)*, Russo said, "Here we see a very high degree of limonene. *(yellow bar, 'Phytoprint' at bottom)*. This might be a chemovar that's very good for treatment of depression, because limonene has that effect. It also is very high in beta-caryophyllene *(blue bar)*. Beta-caryophyllene is a CB2 agonist, a very powerful anti-inflammatory. It also is very low in myrcene, the couch lock compound, so this would be a non-sedating strain that people could use if they have to work or study.

"I think this level of information would be a boon to future consumers."

The essential-oil patterns displayed in "PhytoPrints" suggest a way to define cannabis into classes the way wine is categorized as Merlot, Zinfandel, Pinot, etc.



THE LAUNCH OF PHYTECS

Russo's new employer aims to develop natural products (some cannabis-based)

Ethan Russo was on the agenda twice at the ASA meeting. One talk, drawing on his experience at GW Pharmaceuticals, explained the steps involved in getting U.S. Food and Drug Administration approval for Cannabis-based medicines. Russo expects Epidiolex to "sail through" the FDA approval process. "If you have the right preparation with the right ingredients," he said, "you can make this a very acceptable medicine." Clearly he did not leave the UK company because of misgivings about the practicality of their research agenda.

In Russo's keynote address there were hints of the approach he plans to pursue in his new role as medical director of a start-up called Phytecs. (The name is synthesized from *phyto,* which is Greek for "plant," plus *e*ndo*c*annabinoid *s*ystem.)

According to its website, launched quietly in late February, Phytecs will evaluate beneficial plants other than *Cannabis* that "produce compounds that interact with the endocannabinoid system in many different ways, from mimicking endocannabinoids to slowing or accelerating the enzymes that metabolize them."

Initially, the company plans to develop cosmetics, skincare products, nutraceuticals, and food supplements — "natural products" that can be marketed to consumers after an FDA approval process that does not involve clinical trials. Although it cannot be claimed that natural products are medicines, consumers may discover, for example, that a CBD-rich skin cream is a better (not to mention safer) treatment for acne than FDA-approved Accutane.

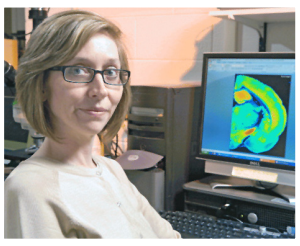
Phytecs, according to Gary Hiller, the Los Angeles attorney who launched it, was inspired by a speech to the International Cannabinoid Research Society by Raphael Mechoulam entitled "Planning Research for the Next Half a Century." Mechoulam suggested that investigators explore new applications for CBD, the uses of the CB-2 receptor, and the role of numerous fatty acids that are close chemical relatives of the body's own cannabinoids.

Hiller engaged Mechoulam as Phytecs' Director of Global Research, and will support trials of semi-synthetic cannabinoids developed in Mechoulam's lab at Hebrew University in Jerusalem.

Phytecs's advisory board includes scientists Heather Bradshaw, Andrea Hohmann and Jürg Gertsch, ethnbotanist James A. Duke, and former Congressman Tony Coelho, who introduced the Americans with Disabilities Act.

Bradshaw runs a lab at Indiana University that has been trying to determine the cause, at the receptor level, of endometriosis and other disorders affecting female reproductive function.

Hohmann also directs a lab at IU that has been focused on the role of the endocannabinoid system in processing pain. "Her laboratory first demonstrated that activation of



ANDREA HOHMANN

CB2 receptors suppresses the processing of nociceptive information," says her Phytecs resume. "Her lab also demonstrated that endogenous cannabinoids are mobilized in the brain underlying a phenomenon known as stress-induced analgesia. This work identified the enzyme monoacylglycerol lipase as a previously unrecognized analgesic target."

Gertsch, now a professor at the University of Bern in Switzerland, determined that beta-caryophyllene in Echinacea exerts effects through the CB-2 receptor. His current research, according to the Phytecs site, "focuses on molecular pharmacology of the endocannabinoid system and drug discovery."

JÜRG GERTSCH

The site provides an intriguing list of plants known to contain beneficial compounds that might be incorporated into balms of various kinds. *(See next page.)* We know that at least one of them makes beneficial compounds, and that cosmetics and nutraceuticals derived from it will be available in Costco sooner rather than later.

"Phytecs is focused not on the arrow, cannabis, but on the target —the endocannabinoid system and other lipid mediators throughout the body and into the microbiome in the gut, where we now know there is interaction between our bodies and the microbes that inhabit us through lipid signaling mechanisms!"
—Michael Backes

"Phytecs is focused not on the arrow, cannabis, but on the target," said Michael Backes, auteur of the Phytecs website at a Society of Cannabis Clinicians meeting in March. He defined the target as "the endocannabinoid system and other lipid mediators throughout the body and into the microbiome in the gut, where we now know there is interaction between our bodies and the microbes that inhabit us through lipid signaling mechanisms!"

Phytecs, said Backes, is "going to cast a very wide net that extends beyond cannabis. We've identified more than 20 genera of plants that have species within them that exhibit endocannabinoid-system activity —not just activating receptors, but interfering with any part of the process of synthesis and metabolism.

Common Name	Terpene Super Class	Secondary Terpene	Tertiary Terpene
Big Sky	Caryophyllene	Humulene	Limonene
Bubba Kush	Limonene	Caryophyllene	Linalool
OG Kush	Limonene	Caryophyllene	Myrcene
Purple Urkle	Myrcene	Caryophyllene	Pinene
Jack Herer	Terpinolene	Caryophyllene	Humulene
Trainwreck	Terpinolene	Myrcene	Limonene
Blue Dream	Pinene	Myrcene	Caryophyllene

Characterizing California Cannabis Strains

By Mark Lewis

Cannabis medicines are currently described by common names, such as "OG Kush, "Purple Urkle," "Trainwreck" et al. Although colorful, these names tell a patient nothing about the chemistry of the plant, and rarely do they convey the anticipated entourage effects.

Names can be meaningless and inconsistencies in naming and production are a major concern in the unregulated medical cannabis industry. In my lab, NaPro Research, the solution was to create a shorthand system of nomenclature to describe cannabis medicines based on their chemistry instead of a common name.

Since 2011 we have analzyed thousands of cannabis samples by gas chromatography for growers and plant breeders in California. (*Giese et al*., submitted for publication 2014 *JAOAC)*. It soon became clear that these connoisseurs relied heavily on their sense of smell when determining the "most correct" common name.

Knowing that smell and entourage effects are related, we looked at the relative essential oil content of each cannabis sample. In due course, classes began to emerge in a continuum of relative phytochemical concentrations. In many cases, the classes aligned with what connoisseurs have traditionally defined as an "OG," a "Purp" or a "Trainwreck."

Contrary to conventional wisdom, common names can be used to distinguish different cultivars, but only when they have been named correctly by cultivators and dispensaries savvy enough to elucidate chemical differences based on aroma and morphology. This isn't always the case, unfortunately, and incorrect names are often applied to samples.

The bottom line is that *Cannabis* genotyping based on secondary-metabolite concentration is a plausible solution to finally ending the naming game.

Product variability is inevitable.

Bear in mind that Grower Andrew's OG might not be the same as Grower Betsy's OG —even if their clones were from the same mother plant. Environment impacts phenotype, and plants with identical genotypes can produce drastically different phenotypes and chemotypes (finished products) when grown or processed in different settings. Cannabis is an agricultural crop and product variability is inevitable.

Keynote *from previous page*

But the problem is worse than that, I'm afraid. A recent paper by R.P. Jensen in the *New England Journal of Medicine* reported that some e-cigarettes using propylene glycol and glycerol as propellants get hot enough to produce large quantities of formaldehyde —a Group 1 carcinogen. This could result in a cancer risk 15 times greater than posed by smoking cigarettes

The researchers were using nicotine in e-cigarettes, but cannabis in a vape pen using propylene glycol as the propellant would pose the same risk. Propylene glycol is nontoxic for humans taken orally in small amounts, but not when it is heated and inhaled.

Cannabis does have side effects. Any time somebody starts an argument by saying, "Cannabis has no side effects," they've already lost. This is something you should never say because it's just simply not true. The truth is that it has some side effects but they're largely avoidable.

According to a tabulation put together by Mark Ware and his colleagues some years ago, neurologic and psychiatric side effects are not uncommon. High-THC preparations cause anxiety, euphoria, decreased muscle tone (which can be useful if spasticity is present), effects on movement, heightened sensory perception, decreased short-term memory, possible sedation, and decreased body temperature. Some people get cold because the set point in the hypothalamus goes down.

People who aren't used to cannabis can easily get too high on a single dose, particularly with a vape pen. Some people take one inhalation on a vape pen and instantly lose consciousness due to orthostatic hypotension. The heart rate slows down so much that there's no oxygen to the brain.

Again, although, cannabis does not cause cancer when smoked, it is inarguable that it produces cough and symptoms of bronchitis.

In the early stages of the Sativex development program, very high doses and very rapid titrations were allowed. What was found was, after a certain number of sprays per day, maybe 10 to 12, there wasn't a big improvement in efficacy, but there was a big increase in side effects.

"The best dose is the lowest dose that improves symptoms... Remember, for proper dosing, 'Start low and go slow.'"

What we know now is that the best dose is the lowest dose that improves symptoms. If you get to the point of overt psychoactivity, it's not necessarily going to be more effective therapeutically. GW Pharmaceuticals found that giving lower doses of Sativex with lower titration reduced dizziness from 32 percent to 14 percent.

Other side effects such as fatigue, somnolence, sleepiness, nausea, dry mouth, all almost disappear. The bottom line is, you got a much better safety profile and efficacy – improvement – by using lower doses and moving slowly. So we will amend the prior statement: Cannabis does have side effects, but they are better than those of any medicine that you see advertised on TV.

Remember, for proper dosing, "start low and go slow."

Finally, in closing: It is critical to understand that cannabis is a plant that modulates the endocannabinoid system (ECS), an innate homeostatic regulator of human physiology. The ECS can also be influenced by lifestyle and dietary factors beyond cannabis. Paramount among these would be low-impact aerobic exercise, and an anti-inflammatory/antioxidant diet.

Thank you!

ETHAN RUSSO AT YANGHAI TOMBS in 2008, near Turpan, Xinjiang, in western China. He assisted in the re-excavation of the tomb of a Gushi shaman who had been buried with a massive stash of cannabis. Photo by Hong-En Jiang, PhD.