"Is this the best way we can grow our big orchards?"
—Woody Guthrie

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The Journal of Cannabis in Clinical Practice

Autumn 2011

Ethan Russo reviews the evidence

Terpenoids, 'minor' cannabinoids contribute to 'entourage effect' of Cannabis-based medicines

By Fred Gardner

The chemical structure of tetrahyrdocannabinol (THC) was determined in 1964 by Raphael Mechoulam and Yechiel Gaoni. For more than three decades thereafter, the blatant psychoactivity of THC induced scientists to define it as the active ingredient in the plant.

Experienced marijuana smokers who tried the drug Marinol (pure, synthetic THC) when it became prescribable in the mid-1980s reported that the effects were dissimilar. But it wasn't until the late 1990s that the research establishment acknowledged that another compound, cannabidiol (CBD), also exerted effects when present in significant amounts.

In 1999 a British start-up, GW Pharmaceuticals, began clinical trials of a whole-plant extract containing roughly equal amounts of THC and CBD. Multiple Sclerosis patients found the combination extract —dubbed "Sativex"— more effective in reducing pain and spasticity than a high-THC extract devoid of CBD, and less psychoactive.

Sativex has now been approved for use by MS patients in England, Canada, New Zealand, and a growing list of European countries. CBD is no longer referred to as a "minor cannabinoid" at scientific conferences and in the literature.

Several cannabinoids still considered "minor" —tetrahydrocannabavarin (THCV), cannabigerol (CBG) and cannabichromene (CBC)— also show therapeutic promise, according to recent studies. Plants with high levels of each have been grown out in GW Pharmaceuticals' glasshouses for research purposes.

Wake up and smell the terpenes!

Scientists are now formally acknowledging something else that Cannabis consumers have long taken for granted: aroma is associated with effect.

The aroma of a given plant depends on which terpenoids predominate.

Plant cannabinoids —21-carbon molecules found only in Cannabis— are odorless. It's the terpenoids —components of the plant's "essential oils"— that create the fragrance. Terpenoids contain repeating units of a 5-carbon molecule called isoprene and are prevalent in smelly herbs such as mints and sage, citrus peel, some flowers, aromatic barks and woods.

The aroma of a given plant depends on which terpenoids predominate. They tend to be volatile molecules that readily evaporate, and they're very potent —all it takes is a few reaching the nose to announce their presence.

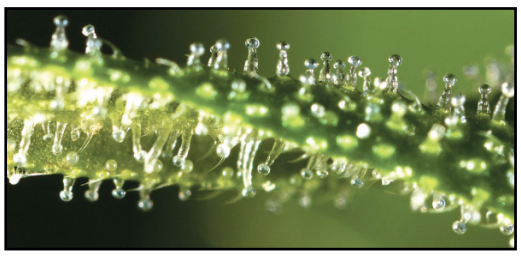
Evidence that "phytocannabinoid-terpenoid interactions" enhance the therapeutic effects of cannabis was presented by Ethan Russo, MD, at a conference in Israel last fall and published in the August 2011 *British Journal of Pharmacology*. Russo, a neurologist and ethnobotanist, is senior medical adviser at GW Pharmaceuticals.

Hergenrather expects Russo's talk to "generate great interest in terpenes among medical cannabis users as well as physicians."

Both terpenoids and cannabinoids are secreted inside the Cannabis plant's glandular trichomes, and they have a parent compound in common (geranyl pyrophosphate). More than 200 terpenoids have been identified in Cannabis. The most common and most studied include limonene, myrcene, alpha-pinene, linalool, beta-caryophyllene, caryophyllene oxide, nerolidol and phytol. Anecdotal evidence suggests that pinene is alerting, limonene "sunshine-y," and myrcene sedating.

The fact that most terpenoid compounds are common components of the human diet and "generally recognized as safe" by the Food and Drug Administration has made research possible, and scientists employed by flavor and fragrances manufacturers have investigated their properties over the years. But the terpenoids "remain understudied" in terms of therapeutic potential, according to Russo.

His paper mustered all the evidence —proof in some cases, hints in others— that cannabinoids and terpenoids



Glandular trichomes (globules atop stalks) contain specialized cells that secrete both cannabinoids and terpenoids.

can work in concert to abate symptoms of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections, including methicillin-resistant Staphylococcus aureus (MRSA, which kills more Americans nowadays than AIDS) and other illnesses.

Jeffrey Hergenrather, MD, president of the Society of Cannabis Clinicians, who heard Russo's presentation in Israel, expects its publication to "generate great interest in terpenes among medical cannabis users as well as physicians." The SCC recently began collecting data on patients' responses to CBD-rich Cannabis. Future surveys will seek to document which other cannabinoids and which terpenoids are associated with which effects.

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Ethan Russo, Raphael Mechoulam, and Yechiel Gaoni at the "Cannabinoids in Biology and Medicine" workshop held at Hebrew University in Jerusalem last November. The event honored Mechoulam on his 80th birthday. His many accomplishments include helping to discover the structure of CBD (with Shvo in 1963), THC (with Gaoni in 1964), and anandamide, the neurotransmitter that THC mimics (with Devane in 1992). A 1998 paper by Shimon Ben-Shabatt, co-authored by Mechoulam, proposed that endocannabinoids (made in the body) act in concert with other compounds to exert an "entourage effect." Russo, a senior medical advisor with GW Pharmaceuticals, applied the entourage concept to phytocannabinoids (made by the plant). photo by Lumir Hanus

Bracts on cannabis flowers are sites of most abundant trichome production.

Project CBD Update—

starts on page 7

• CBD-Rich Strains Abound

Some 35 strains containing more than 4% Cannabidiol have been identified by labs serving the medical cannabis industry in the U.S.

• SCC Launches Survey

The Society of Cannabis Clinicians has begun collecting patients' responses to CBD-rich products.

• How CBD Works

Martin A. Lee lays out what scientists have learned about the mechanism of action by which CBD exerts its effects.

• "Sour Tsunami" Stabilized

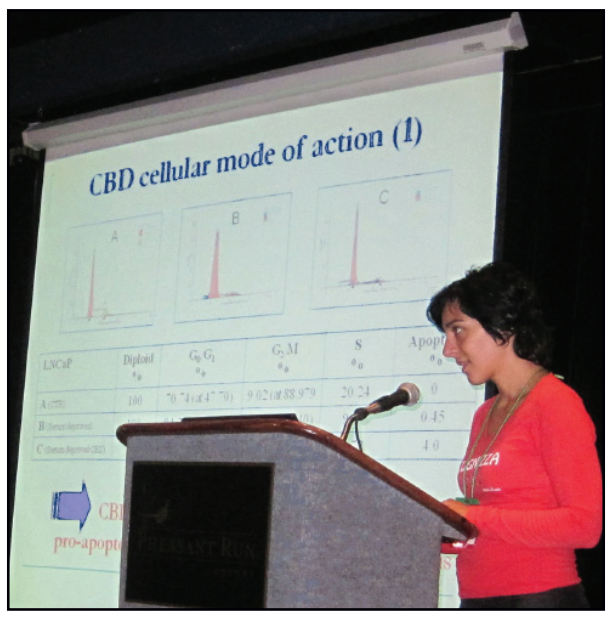
Lawrence Ringo (below) has bred plants that produce seeds with a one-in-four chance of containing 10-11% CBD (and 6-7% THC)!

• Harlequin, Omrita Rx3 Clones Released

To expedite patient access to CBD-rich medicine, the developers of two remarkable strains have chosen to make clones available (rather than provide only flowers) to dispensaries participating in Project CBD.

• ICRS 2011: CBD Research Accelerates

"CBD was the star of the show on opening day here at ICRS, demonstrating potent anti-cancer effects in a variety of cancer types." —*Jahan Marcu, on the International Cannabinoid Research Society meeting in early July.*



Alessia Ligresti's ICRS talk described "Mechanisms of the anti-cancer effects of cannabidiol and other non-psychotropic cannabinoids on human prostate carcinoma." Her team studied 12 cannabinoids in pure form and in "relative enriched extracts" (in each of which a different cannabinoid was predominant). They observed, "Generally, among all pure compounds tested, CBD was the most efficacious at reducing cell viability... and in many cases the [extracts] were more potent than pure compounds." CBC and CBG were also found to be effective, but "to a lesser extent." Prostate cancer cells are killed, Ligresti reported, "through several concurring molecular mechanisms." An entourage effect!

Entourage Effect *from page 1*

The "Entourage Effect"

The conference at which Russo presented his paper was held at Hebrew University, Jerusalem, where Raphael Mechoulam directs a lab, in honor of Mechoulam's 80th birthday.

In 1999 Mechoulam co-authored a paper with Shimon Ben-Shabat suggesting that cannabinoids made in the body work by means of an "entourage effect." They had found that the endocannabinoid 2-AG (2-arachidonoylglycerol), when administered with two related compounds, would bind more readily at the cannabinoid receptors and exert more pronounced behavioral effect on mice.

To pharmacologists who customarily designed experiments aimed at finding *the* active ingredient, this had heavy implications. Mechoulam spelled them out: "Biochemically active natural products, from either plant or animal origin, are in many instances accompanied by chemically related though biologically inactive constituents. Very seldom is the biological activity of the active constituent assayed together with inactive 'entourage' compounds. Investigations of the effect of the active component in the presence of its 'entourage' compounds may lead to results that differ from those observed with the active component only."

> *"Very seldom is the biological activity of the active constituent assayed together with inactive 'entourage' compounds."*
>
> *—Raphael Mechoulam*

In 2001 John McPartland and Russo published a paper in the *Journal of Cannabis Therapeutics* applying the "entourage" concept to the plant itself. "Good evidence shows that secondary compounds in cannabis may enhance the beneficial effects of THC... and reduce THC-induced anxiety, cholinergic deficits, and immunosuppresion," they wrote. "Cannabis terpenoids and flavonoids may also increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens, and provide anti-inflammatory activity."

A decade later, Russo is substantiating the molecular-teamwork hypothesis and expanding on it. His *BJP* paper, "Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects," contains 304 citations.

Although the paper takes the form of a review of the literature, Russo's perspective is forward-looking and practical. The paper can be read as a strategic guide for breeding and/or blending Cannabis so as to maximize specific medical effects. Its structure is straightforward:

1. Russo cites studies documenting the beneficial effects of THC, CBD, CBC, THCV, CBDV, CBG and CBN (noting the adverse effects attributed to THC).

2. He cites studies documenting the beneficial effects of Limonene, α-Pinene, Myrcene, Linalool, β-Caryophyllene, Caryophyllene Oxide, Nerolidol, and Phytol.

3. He notes which cannabinoid effects would be augmented by which terpenoids, and which terpenoid effects would be augmented by which cannabinoids.

There is a huge body of information to convey, and Russo's style is compressed —documented fact after documented fact after documented fact, with insights positioned fittingly. The slides he showed in Israel have been integrated into two full-page tables for the *BJP* paper, listing the relevant studies and the cannabinoid-terpenoid combinations likely to produce a desired effect. The paper, online at http//onlinelibrary.wiley.com/doi/10.111/j.1476-5381.2011.01238x/abstract, is well worth reading. Our summary and the disjointed highlights that follow cannot do justice to Russo's carefully constructed thesis.

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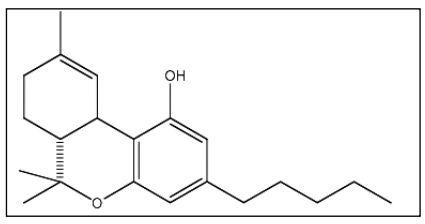
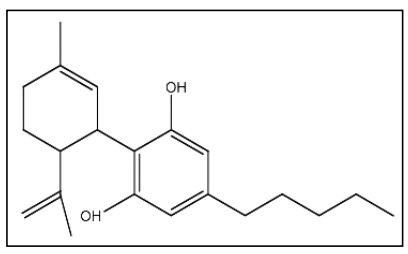
Phytocannabinoid Effects

Δ⁹-tetrahydrocannabinol (THC)



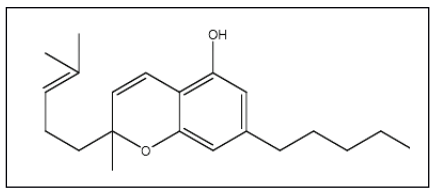
- Analgesic via CB1, CB2
- Antipruritic
- Neuroprotective/Antioxidant
- 20 times the anti-inflammatory effect of aspirin
- Twice the anti-inflammatory effect of hydrocortisone
- Not a Cox-1 or Cox-2 inhibitor
- Reduces amyloid plaque build-up

Cannabidiol (CBD)



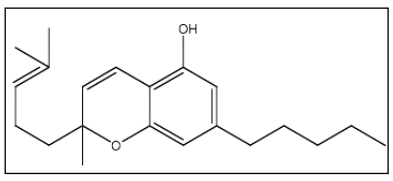
- Neuroprotective antioxidant, strongly inhibits glutamate excitotoxicity; more potent antioxidant than Vitamins C, E
- Inhibits uptake of anandamide, weakly inhibits its breakdown
- Alerting vs. THC
- Anticonvulsant
- Anti-anxiety
- Cytotoxic in breast cancer and many other cancer cell lines; cytopreservative for normal cells
- Antagonist at GPR55 and GPR18
- Antagonizes tumor necrosis factor alpha in rodent rheumatoid arthritis.
- Not Cox-1 or Cox-2 inhibitor
- Agonist at serotonin receptor (why it may counter anxiety)
- Reduces nausea
- Improved cognition in hepatatic encephalopathy
- Enhances adenosine receptor A2A signaling via inhibition of an adenosine transporter, suggesting anti-inflammatory and analgesic role
- Prevents prion accumulation and neuronal toxicity
- Powerful activity against MRSA

Cannabigerol (CBG)



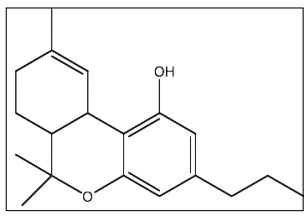
- GABA uptake inhibitor (more potent than THC or CBD)
- Modest antifungal activity
- Antidepressant
- Anti-hypertensive
- Next most effective phytocannabinoid vs. breast cancer after CBD
- Inhibits keratinocyte proliferation (anti-psoriasis?)
- Powerful activity against MRSA
- Analgesic?
- Inhibits anandamide reuptake.
- TRPM8 antagonist (application in prostate cancer?)

Cannabichromene (CBC)



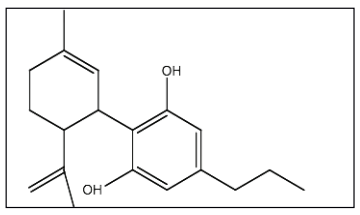
- Anti-inflammatory
- Analgesic (less than THC)
- Antibiotic/antifungal
- Cancer cytotoxic agent
- CBC extract antidepressant in rodents
- Anandamide reuptake inhibitor

Tetrahydrocannabivarin (THCV)



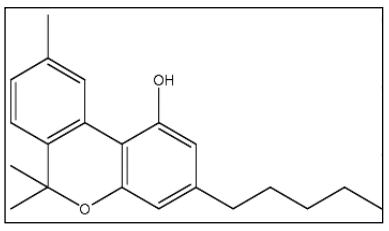
- CB1 antagonist at low doses, but CB1 agonist at higher doses.
- Produces weight loss, decreased body fat, increased energy expenditure in obese mice.
- Anticonvulsant in rodent cerebellum and pyriform cortex.

Cannabidivarin (CBDV)



- Anticonvulsant in hippocampal slices

Cannabinol (CBN)



- Sedative
- Anticonvulsant
- Anti-inflammatory
- Antibiotic, potent against MRSA
- TRPV2 agonist of interest in burns
- Inhibits keratinocyte proliferation (utility in psoriasis?)
- Stimulates recruitment of quiescent mesenchymal stem cells in marrow, promoting bone formation

Inhibited breast cancer resistance protein. Megadoses might help treat breast tumors.

PHYTOCANNABINOIDS AND THEIR EFFECTS were reviewed by Ethan Russo, MD, at the International Workshop on the Cannabinoids in Biology and Medicine, held in Jerusalem, November 2010. Phytocannabinoids are odorless, 21-carbon molecules found only in the Cannabis plant and nowhere else in nature. Russo's slides, excerpted above, cited the studies by which each cannabinoid effect was determined. The relevant studies are also cited in Russo's paper in the August 2011 *British Journal of Pharmacology,* "Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects" —online at http://onlinelibrary.wiley.com/doi/10.1111/j.1476-5381.2011.01238.x/abstract. GW Pharmaceuticals has developed cannabis cultivars in which CBC and THCV are predominant —and one in which the entire cannabinoid content is CBG. GW Pharmaceuticals' plant-breeding program is described on their website and in a four-part series by Etienne de Meijer and co-workers in the journal *Euphytica.*

Entourage Effect *from previous page*

The Cannabinoids
Formerly Known as Minor (CFKMs)

The extensive breeding program directed by GW Pharmaceuticals' Etienne de Meijer has yielded plants rich in CBD, CBC, CBG, and THCV.

Cannabichromene (CBC) is produced early in the plant's life cycle according to a paper published by de Meijer in 2009. Citing de Meijer's co-worker David Potter, Russo notes that "An innovative technique employing cold water extraction of immature leaf matter from selectively bred cannabis chemotypes yields a high-CBC 'enriched trichrome preparation.'"

Cannabigerolic acid (CBGA), the precursor of THC, CBD, and CBC in their acid forms, is usually found at low concentrations. "But recent breeding work has yielded cannabis chemotypes lacking in downstream enzymes that express 100% of their phytocannabinoid content as CBG," according to Russo. (More details are provided on GW Pharmaceuticals' very informative website.)

Tetrahydrocannabivarin (THCV) blocks the CB1 receptor at low doses, and activates it at high doses. GW Pharmaceuticals hopes that a THCV-rich extract will be an effective appetite suppressant and will counter the symptoms of metabolic syndrome.

Every compound the plant produces has or had an evolutionary purpose.

THCV is present in cannabis chemotypes from southern Africa —from which plants that are "highly predominant" in THCV have been bred.

Terpene Factoids

Whereas plant cannabinoids are found nowhere else in nature, terpenoids are produced by countless plant species. Some 20,000 terpenoids have been identified by chemists; they constitute the largest group of plant chemicals. More than 200 have been found in cannabis.

"Essential oil composition is much more genetically than environmentally deter-

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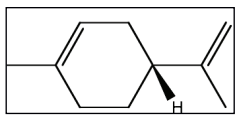
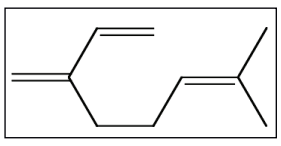
Terpenoid Effects and Synergistic Cannabinoids

LIMONENE (also found in lemon)



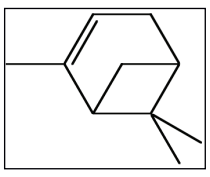
- Antidepressant and immune stimulator in humans —CBD
- Anti-anxiety, antidepressant in mice via serotonin receptor. CBD
- Apoptosis of breast cancer cells —CBD, CBG
- Effective against dermatophytes —CBG
- Gastro-esophageal reflux —THC

MYRCENE (also found in hops)



- Blocks inflammation via prostaglandin E2 —CBD
- Analgesic in mice, antagonized by naloxone —CBD, THC
- Sedating; muscle relaxant; potentiated sleep time —THC
- Blocks hepatic carcinogenesis by aflatoxin —CBD, CBG

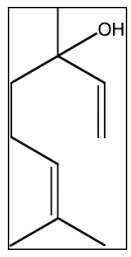
α-PINENE (also found in pine needles)



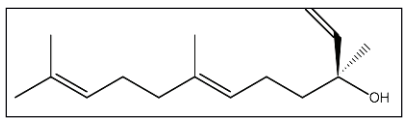
- Anti-inflammatory via prostaglandin E-1 mechanism —CBD
- Bronchodilatory in humans —THC
- Acetylcholinesterase inhibitor, aiding memory —THC?, CBD
- Anti-MRSA *et al* —CBD, CBG, CBN
- Wide-spectrum antibiotic

LINALOOL (also found in lavender)

- Anti-anxiety —CBD, CBG?
- Sedative on inhalation in mice —THC
- Local anesthetic equal to procaine, menthol —THC
- Anticonvulsant/anti-glutamate —CBD, THCV, CBDV
- Analgesic in mice
- May achieve these effects by modulating glutamate and GABA neurotransmission.

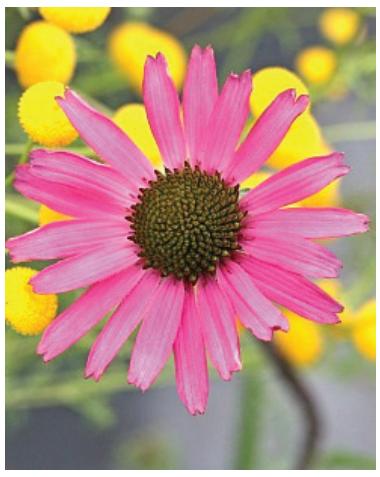


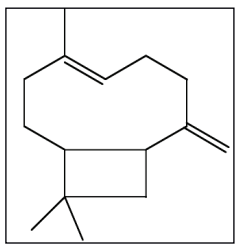
NEROLIDOL (also found in orange)



- Sedative —THC, CBN
- Skin penetrant —?
- Inhibits fungal growth —CBC
- Utility in contact dermatitis?

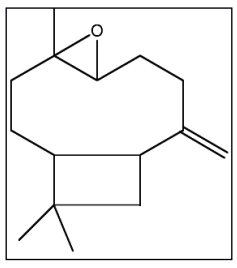
BETA-CARYOPHYLLENE (also found in Echinacea)





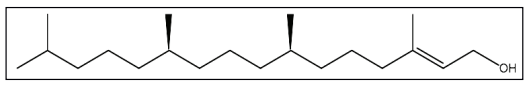
- Anti-inflammatory via PGE-1 —CBD
- Gastric cytoprotective —THC
- Selective CB2 full agonist (anti-inflammatory, analgesic) —THC
- Treatment of pruritus? —THC
- Treatment of addiction? —CBD

CARYOPHYLLENE OXIDE (also found in lemon balm)



- Antifungal in onychomycosis —CBC, CBG
- Insecticidal —THCA, CBGA

PHYTOL (also found in green tea)



- Counters mutagenic effect of Vitamin A
- Blocks breakdown of GABA —CBG

TERPENOIDS COMMON IN CANNABIS, their effects, and synergistic cannabinoids as listed by Russo. Aromatic terpenes abound in smelly herbs such as mints and sage, citrus peel, some flowers, barks and woods. In Cannabis, terpenoids and cannabinoids are produced by secretory cells in the glandular trichomes. Terpenes contain repeating units of isoprene, a 5-carbon molecule. Terpenoid naming is based on 10-carbon units: monoterpenes contain 10 carbons, sesquiterpenes 15, diterpenes 20, etc. Monoterpenes are lightest and evaporate most readily. Thus Cannabis extracts tend to lose myrcene, pinene, and limonene (all monoterpenes) in proportion to beta-caryophyllene (a sesquiterpene). Some 200 terpenoids have been identified in Cannabis, but only those shown here and a few others occur frequently in significant amounts. Russo specified which cannabinoids are likely to augment medically useful terpenoid effects and vice versa. GW Pharmaceuticals has developed a cannabinoid-free cannabis cultivar, which should facilitate investigation of terpenoid effects. See www.GWPharm.com and Meijer EPM de, Hammond KM, Sutton A. 2009, "The inheritance of chemical phenotype in Cannabis sativa L. (IV): cannabinoid-free plants," *Euphytica* 168: 95-112.

Entourage Effect *from previous page*

mined," Russo states. Every compound the plant produces has or had an evolutionary purpose. The bitter 15-carbon terpenoids in the fan leaves repel grazing animals, while the predominantly monoterpene mix in the flowers is unappealing to insects —and, thanks to its stickiness, can also entrap them.

Alpha-pinene is the most common terpenoid in the plant world; limonene is second. Named for their strong presence in pine needles and lemons, respectively, they are monoterpenes, also prevalent in cannabis.

Terpenoids may account for only 1% of the weight when cannabis is tested but 10% of the weight within the trichome.

Monoterpenes evaporate more readily than the di- and sesquiterpenes during drying, storage, and production of extracts, which results in a relatively higher proportion of caryophyllene.

Beneficial Effects

How do terpenoids exert effects within the body? Citing the relevant studies, Russo explains that they are "lipophilic, interact with cell membranes, neuronal and muscle ion channels, neurotransmitter receptors, G-protein coupled (odorant) receptors, second messenger systems and enzymes."

Limonene has been shown to decrease anxiety in mice via the serotonin receptors.

The beneficial effects are wide-ranging and, in many cases, well established. Limonene, for example, has been shown to decrease anxiety in mice via the serotonin receptors. "Compelling confirmatory evidence in humans," Russo writes, was provided by a Japanese study of severely depressed hospital patients whose moods improved when exposed to citrus fragrance. (Nine of 12 were able to get off antidepressants.)

Essential Resource

The Handbook of Essential Oils: Science, Technology and Applications by K. Husnu Can Baser and Gerhard Buchbuaer, is a 975-page compendium published in 2010 By CRC Press, Boca Raton, FL.

Ethan Russo must have made good use of this book. Reviewing it in *Herbalgram,* he wrote, "The antimicrobial activities of the terpenoids are handled with an introduction in which the activity of thymol (an ingredient in Listerine) is stated as 10-fold stronger than phenol. This is followed by an astounding 177 pages of tables documenting previous experimental work examining the effects of various agents."

A chapter on aromatherapy points out the difficulty of conducting randomized clinical trials (RCTs) with substances that have such obviously distinct smells. No RCTs, no "scientific validity."

Limonene, inhaled, is an immunostimulant. In lab experiments it has killed breast cancer cells and acne bacteria. It is a potential treatment for gastro-esophageal reflux.

Alpha-pinene —as anyone who has walked into piney woods and breathed deeply can sense— is a bronchodilator. It also has anti-bacterial and antibiotic properties. α-Pinene inhibits the enzyme that breaks down acetylcholine, a neurotransmitter involved in memory. "This feature could counteract short-term memory deficits induced by THC intoxication," Russo notes.

Myrcene, combined with THC, may produce the 'couch-lock' phenomenon of certain chemotypes.

Myrcene, another monoterpene common in cannabis, is also abundant in the flowers of humulus lupulus —hops— the only other member of the *Cannabinacae* family. In addition to its anti-inflammatory effect, Russo writes, "Myrcene is a recognized sedative as part of hops preparations, employed to aid sleep in Germany... Myrcene acted as a muscle relaxant in mice, and potentiated barbiturate sleep time at high doses.

"Together, these data would support the hypothesis that myrcene is a prominent sedative terpenoid in cannabis, and combined with THC, may produce the 'couch-lock' phenomenon of certain chemotypes that is alternatively decried or appreciated by recreational cannabis consumers."

Linalool has sedative and anti-convulsant properties.

Linalool, which is abundant in lavender, affects serotonin neurotransmission and counters anxiety, according to a study cited by Russo. Linalool has sedative and anti-convulant properties, and is also "the likely suspect in the remarkable therapeutic capabilities of lavender essential oil to alleviate skin burns without scarring."

Beta-caryophyllene, which is found in black pepper, Echinacea, and marigolds, "is frequently the predominant terpenoid in cannabis extracts, particularly if they have been processed under heat." β-caryophyllene is anti-inflammatory and, unlike other anti-inflammatories, protective of the stomach lining.

In 2008 Swiss investigators led by Jurg Gertsch showed that β-caryophyllene activates the CB2 receptor —making it "the first proven phytocannabinoid beyond the cannabis genus," Russo proclaims. "Given the lack of psychoactivity attributed to CB2 agonists, caryophyllene offers great promise as a therapeutic compound, whether systemically or in dermatological applications."

Other terpenoids with therapeutic potential mentioned by Russo in his *BJP* paper are nerolidol (found in citrus, it may have sedative and anti-fungal effects); caryophyllene oxide (found in the herb lemon balm, it repels insects); and phytol (a breakdown product of chlorophyll with relaxant properties that may be the reason that green tea, despite its caffeine content, doesn't jangle the nerves).

In their landmark 2001 paper in the *Journal of Cannabinoid Therapeutics,* Russo and lead author John McPartland touched on the beneficial effects of eucalypytol, pulegone, alpha-terpineol and other possibly efficacious terpenoids. These compounds were not discussed in Russo's 2011 *BJP* paper.

Designer Extracts

Russo describes several mechanisms by which terpenoids and/or cannabinoids can act synergistically.

Cannabis designer extracts are likely to yield safe, effective new treatments for a wide range of conditions

• They can work on separate targets. For example, if CBD were combined with limonene as an acne treatment, the cannabinoid could penetrate the skin and induce the cells that produce sebum to self-destruct, while the terpenoid could inhibit production of the key pathogen, *Propionbacterium acnes*. (Linalool and alpha-pinene also suppress *P. acnes*.)

• They can interact to overcome bacterial resistance. For example, CBD and CBG "powerfully inhibit MRSA," according to one study cited by Russo, while in another study, an essential oil rich in pinene proved "as effective against MRSA and other antibiotic resistant bacterial strains as vancomycin."

• They can have an antagonistic effect, as in the case of CBD countering THC's ability to promote an accelerated heartbeat, the munchies, drowsiness, and anxiety.

Key role for CBD

CBD will play a key role in extracts designed for medical use. Although deemed "non-psychoactive," CBD reduces anxiety by affecting the serotonin receptors. It also reduces cravings —for heroin, cocaine, food, nicotine and other addictive substances.

Russo describes a recent study that "demonstrated the fascinating result" that stroke patients who had suffered damage to a part of the brain called the insula "were able to quit tobacco smoking without relapse or urges."

"In a provocative parallel," he adds, functional MRIs of patients given CBD (600 mg p.o.) dramatically reduced activity observed within the left insula "suggesting the possibility that CBD could act as a pharmaceutical surrogate for insular damage in exerting an anti-addiction therapeutic benefit."

Which terpenoid(s) would be complementary? Citing a study in which inhaled-vapor from an essential oil of black pepper reduced craving for cigarettes, Russo writes: "the terpene profile of black pepper suggests possible candidates: myrcene via sedation, pinene via increased alertness, or especially caryophyllene via CB2 agonism."

Is Irradiation Safe?

Russo's *BJP* paper contains an assertion, tangential to his theme, that seems like a big story in and of itself: "Government-approved cannabis supplied to patients in national programs in the Netherlands and Canada is gamma-irradiated to sterilize coliform bacteria, *but the safety of this technique for a smoked and inhaled product has never been specifically tested."* (Emphasis added by *O'Shaughnessy's*.)

Russo cites studies showing that "Gamma-irradiation significantly reduced linalool titres in fresh cilantro, and myrcene and linalool in orange juice."

In other words, getting zapped with-gamma rays may not only make plants unsafe to inhale, it can reduce their nutritional value.

The Research Agenda

Cannabis designer extracts are likely to yield safe, effective new treatments for a wide range of conditions, and —in due course, it is hoped— to regulatory approval and sales. GW Pharmaceuticals has already bred cannabis chemotypes with very high fractions of myrcene and limonene, and we assume they're working on plants high in pinene, linalool and other terpenoids with therapeutic potential. As Russo puts it in his *BJP* paper, "Selective cross-breeding of high-terpenoid- and high-phytocannabinoid-specific chemotypes has... become a rational target."

Meanwhile back in California, research-minded doctors, cannabis cultivators, dispensary and lab owners, have been thinking along similar lines. (The idea that cannabis can be bred to maximize production of more than one compound is as obvious as the association between aroma and effect.) We don't have the resources to do high throughput pharmacological screening or animal studies involving radioactive labeling, but we do have access to labs that can identify the compounds in a cannabis bud, and we have our own senses to evaluate effects.

As *O'Shaughnessy's* goes to press in late August, we know of two labs in California that have begun testing for terpenes and others are maing plans to do so. *(See story on next page.)* ProjectCBD.org and cannabisclinicians.org will carry updates on what we, collectively, are about to learn.

RAPHAEL MECHOULAM in the fall of 2010, addressing scientists assembled in his honor. Ethan Russo paid homage to a 1999 paper in which Mechoulam used the term "entourage effect" to describe how compounds act in concert to activate receptors in the body. Mechoulam commented in that paper, "This type of synergism may play a role in the widely held (but not experimentally based) view that in some cases plants are better drugs than the natural products isolated from them." PHOTO BY ZACH KLEIN