

At the IACM Meeting

Russo Previews What's in the Organic Pipeline

Economic catastrophe looms for the pharmaceutical industry as many of its synthetic money-makers are being exposed as dangerous and/or losing patent protection. Very few promising synthetics are in the manufacturers' pipelines.

The cannabis plant, on the other hand, has been shown to contain numerous compounds with medical potential.

Evidence that cannabinoids other than THC and CBD exert biological effects—as do the terpenes that give cannabis its fragrance—was reviewed at the IACM meeting by Ethan Russo, MD. Russo is a neurologist employed by GW Pharmaceuticals, a researcher, author, and a clear expositor.

Cannabinoids and terpenes are produced and stored in the glandular trichomes of the plant. They share a biosynthetic parent—geranylpyrophosphate (GPP)—and are “half-siblings,” Russo explained.



Cannabinoids “in the raw” take the form of carboxylic acids (meaning they have a -COOH group at a certain position on the molecule). This carboxyl group is unstable; heat and light make it evaporate as CO₂, resulting in neutral cannabinoids. Thus THCA is converted to THC when cannabis buds are vaporized or baked.

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Just as Mechoulam had described a very promising epilepsy study by Consroe *et al* in the 1980s that did not lead to further research, Russo made reference to numerous past studies that attributed significant health benefits to the “minor” cannabinoids and terpenes but were never followed up on.

He described **cannabichromene (CBC)**, for example, as “a strong anti-inflammatory agent—but that hasn't been examined in recent decades... CBC is analgesic (less so than THC)... Antibiotic, antifungal. Also, a potent cancer

Endogenous Cannabinoid Deficiency

Ethan Russo also gave a talk at the IACM meeting on “endogenous cannabinoid deficiency,” which could result from a diminished number of cannabinoid receptors or the insufficient presence of anandamide and other endocannabinoids. Whatever the causes, Russo postulates that “clinical endocannabinoid deficiency” underlies migraines, fibromyalgia, irritable bowel disease, and other degenerative illnesses, which may respond favorably to cannabinoid remedies.

Individuals have different congenital endocannabinoid levels and sensitivities. A surplus or lack of metabolic enzymes involved in the formation and breakdown of anandamide could skew the endocannabinoid system. And dietary factors may also contribute to endocannabinoid deficits. Essential fatty acids (abundant in hempseed, flaxseed, walnuts and fish) are biochemical precursors of anandamide; a diet low in omega oils can compromise the endocannabinoid system. —Martin Lee

cytotoxic agent much like CBD. It's cytoprotective for normal cells.” Work with mice by Rik Musty at the University of Vermont showed that CBC has antidepressant effects and that it counters THC toxicity. Russo said that GW has developed a CBC-rich cannabis cultivar and has begun researching its properties intensively.

“**Cannabigerol (CBG)** is a GABA uptake inhibitor more powerful than THC or CBD—which could explain its anti-anxiety effects... A muscle relaxant... an analgesic stronger than THC... Antibiotic, antifungal... In tests a few years ago it was effective against oral epithelial carcinoma at very high doses—but since there's no apparent toxicity, such high doses might be possible.”

GW has developed a cannabis plant that produces CBG alone. CBG inhibits the proliferation of keratinocyte cells, which raises the prospect of a treatment for psoriasis.

Cannabinol (CBN) has weak activity at the CB2 receptor. It's a THC oxidation product that some cultivars express as they age (and as they degrade in storage). Musty has found CBN to have anticonvulsant, anti-inflammatory, and antibiotic effects.

Beyond Cannabinoids

The terpenoids, like the cannabinoids, defend the plant against predators. Limonene and *alpha*-pinene are insect repellants (identified as such by John McPartland). CBG acid and THC acid are known induce cell death in insects.

Terpenoids are present in small amounts but are very potent. Terpenoids are derived from 5-carbon isoprene units and come in different flavors: monoterpenoids (10 carbon, 2 isoprene units), sesquiterpenoids (15 carbon, 3 isoprene units), diterpenoids (20 carbon, 4 iso-

prene units) and triterpenoids (30 carbon, 6 isoprene units).

Limonene, which gives citrus its characteristic scent, is a monoterpene (10 carbon atoms) from which various terpenoids are synthesized by steps not yet worked out. “If there's a grad student needing a project it would be the biosynthetic pathway of terpenoids in cannabis,” Russo offered. Russo called limonene “a potent anti-depressant” and described a study in which a citrus scent wafted onto a psychiatric ward enabled people to get off anti-depressants.



Ethan Russo

Myrcene is an analgesic that probably works on the opioid receptor system. (It's effects are blocked by naloxone, an opioid antagonist.) Myrcene is also anti-inflammatory, sedating, a muscle relaxant. One study involving mice showed that it potentiates the sleep-inducing effects of barbiturates. Myrcene also blocks the cancer-causing effects of aflatoxins (from the fungus on peanuts).

Linolool, a component of lavender, is an anti-anxiety agent. It has sedative effects when inhaled by mice at low dose. It's also, according to Russo, a local anesthetic and anticonvulsant.

Pinene has anti-inflammatory and bronchodilatory properties. “If you go into a pine forest for a walk to clear your head it's probably a very real pharmacological effect,” Russo said. Several studies indicate that it enhances memory by inhibiting acetylcholinesterase

Beta-caryophyllene is the most frequent sesquiterpene or 15-carbon terpene

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in cannabis. It is anti-inflammatory and protects the lining of the GI tract (in contrast to non-steroidal anti-inflammatories). It has antimalarial properties. Russo summarized the finding presented by Gertsch at the ICRS meeting that Beta-caryophyllene is a potent selective CB2 agonist.

Nerolidol is a trace element in citrus rinds, a sesquiterpene alcohol that Russo said “easily gets through the skin and is used to drag other things in.” It has sedative and anti-malarial properties.

Caryophyllene oxide, the chemical by which sniffer dogs identify cannabis, decreases platelet aggregation. As an antifungal, Russo said, it is “comparable to standard agents in its ability to treat nail infestations.” He foresees potential for an insecticide that would be non-toxic to humans. (Caryophyllene oxide is an FDA-approved food additive.)

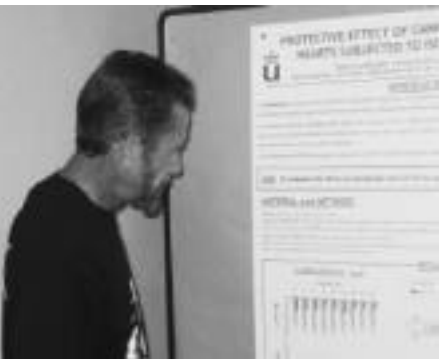
Phytol is a diterpene with 20 carbons—a breakdown product of chlorophyll that Russo described as “ubiquitous—any dried spice or vegetable matter is likely to have some phytol.” It is known to prevent certain congenital malformations. Russo said that phytol “has some sedative influences and might be the reason why so many teas are considered relaxing. Very little work [has been] done on it despite how common it is.”

Flavonoids are also active ingredients in cannabis. “Flavonoids are up and coming in phyto-medicine,” Russo said, “because they're very strong in anti-oxidants that may have a role in preventing aging.” He singled out **apigenin**, a flavone known to be “a very effective non-sedating anti-anxiety agent—probably the active agent in chamomile, the reason that it's a relaxing tea... It's also anti-inflammatory via inhibition of tissue necrosis factor-alpha, which might make it useful in treating MS or rheumatoid arthritis.”

Russo also mentioned **cannflavin-A**, which might work to reduce fever (by inhibiting release of prostaglandin E2 by blood vessel walls in response to infection). Russo called cannflavin A “an effective anti-inflammatory agent that's unique to cannabis. But it's had no recent investigation.”

Asked to sum up the evidence that compounds present in such minute quantities in cannabis could be exerting strong effects, Russo cited inhalation experiments in rodents that produced measurable serum-level changes, and widespread reports by medical cannabis users that different strains produce markedly different effects. “We know that most North American cannabis is pretty much all THC,” Russo said. “Where do the strain differences come from? They've been ascribed to different cannabinoid ratios, but if it's all THC, the difference has to come from terpenes.”

IACM Scrapbook



Clockwise from bottom left: IACM founder Franjo Grotenhermen (lying down due to balance problem) and newly elected chairwoman Kirsten Mueller-Vahl; Robert Sterner; Rudolf Brenneisen and Arno Hazenkamp; Jeffrey Hergenrather, Dale Gieringer, and Raphael Mechoulam; Daniela Parolaro and Hergenrather; Clare Hodges and Willie Notcutt.