

Ethan Russo, MD Interview with Martin Lee of ProjectCBD.org "*CBG, Cannabinoid Acids, And The Global CBD Phenomenon*"

**Lee:** Welcome to another edition of cannabis conversations. I'm Martin Lee with project CBD and today we will be speaking to Dr. Ethan Russo, a noted neurologist, a researcher in the cannabis field for many years and author of quite a few peer reviewed scientific papers. Dr. Russo. I recall reading your articles in various scientific journals about a CBD, Cannabidiol, many years ago. And yet today, now we are in the midst of a CBD explosion. It has become a huge global phenomenon. As a researcher who's looking at CBD much earlier than in the culture has embraced it, how do you relate to this cultural phenomenon?

**Russo:** Well, I was aware of the psycho-pharmacological effects and other effects of Cannabidiol from the early seventies. That was one of my interests, in my early education. At that time it was relegated to the back seat, at best, in relation to THC, which garnered all the attention.

Certainly in medical school there was no attention to this topic at all. However, as developments accrued there was the discovery of the Endocannabinoid system, which rekindled my interest in the mid nineties, when I really delved back into the pharmacology of cannabis. It was apparent to me that a very important pharmacological agent had been overlooked. That being CBD. I was

then quite aware of its potential medically, which had been largely forgotten outside of professor Mechoulam and his acolytes and perhaps the Brazilians, who had studied the properties of CBD as an anticonvulsant. When I began my work with GW Pharmaceuticals in 1998, they had been prescient to realize that this was a very important component of a properly constituted cannabis preparation to be used therapeutically. So, it was like an equal partner to THC in their development program.

At that time the company was also funding basic research into investigate additional attributes of CBD, particularly as an anti-inflammatory and as an analgesic / painkiller, and its ability to reduce the side effects of THC. Along with interest and other components, I began writing about CBD.

**Lee:** Did you ever imagined it would get to this point where CBD would be this cultural artifact almost?

**Russo:** Well, I always hope so. It was a well deserved status to finally be recognized for what it could actually do. Lee:

So cannabis has been described by Dr. Mechoulam in Israel as a medicinal treasure trove. And I assume he's not just talking about THC and CBD two of the major components of the plant. What else is in the plant that we should be paying attention to and what else might become available to patients and consumers as something that can be used therapeutically?

Well, we're seeing history repeated. So all the attention has been on THC and CBD, to the exclusion of what may be as many as 148 different cannabinoids that the plant produces, which seemingly are unique to cannabis, although we've got a couple of exceptions from nature. On the horizon, certainly I think Cannabigerol, CBG, which is the parent molecule to THC and CBD, has great potential.

Oddly, CBG is not an intoxicating agent. It does have a strong anti-anxiety effect. And for people who have access to it, this is an almost universal descriptor of the effects. Beyond that, it seems to be a powerful antibiotic that can work on bacteria that are normally resistant to antibiotics, especially Methicillin Resistant Staph aureus, which has caused some hospital acquired, infections and deaths. Particularly in the immunocompromised patient, this is potentially fatal. Additionally, CBG, works on a variety of cancers, especially prostate cancer, where it seems to have a specific effect. CBG could be leveraged into an important medicine for, prostate cancers, one of the main killers of older men. So it's of interest to us because of our age demographic. CBG is an extremely promising agent.

Finally, after again being ignored for decades, the acid cannabinoids that are actually produced in the cannabis plant, CBDA (Cannabidiolic acid) and THCA (Tetrahydrocannabinolic acid) the naturally produced precursors to THC and CBD, created through a process called decarboxylation or the loss of a CO<sub>2</sub>

molecule, as the result of heating, either by smoking, vaporizing, baking, or in the lab. These compounds [CBDA and THCA] were relegated to be inactive in the past, but they just weren't looking in the right places or didn't have the right tools at the time. About 15 years ago, THCA was shown to have activity on tumor necrosis factor alpha, TNF alpha for short. This is an important mediator of auto-immune effects. So it's important in diseases like multiple sclerosis, rheumatoid arthritis, ulcerative colitis and Crohn's disease. Probably as well as a lot of other autoimmune diseases that we're seeing increasingly in our populations.

As if that weren't enough though, a couple of years ago, a group in Spain identified THCA as seemingly the most powerful of the cannabinoid agents on another receptor. THCA was shown to be an agonist, a stimulator of the P-PAR gamma receptor. which is a nuclear receptor, affecting gene transcription, how the inner workings of the cell really work. Now that sounds scary, although there are a lot of very important potential therapeutic effects from that, including helping with weight loss, the metabolic syndrome, type two diabetes and treating cancer. So what we're seeing now is the science is actually catching up with people who have been using raw cannabis, particularly THCA to treat a variety of conditions. And we knew before that a lot of patients with autoimmune conditions were getting benefit from raw cannabis products.

So the other side of the coin is CBDA, Cannabidiolic acid, the precursor in the plant to CBD. One of the effects of CBD that was discovered in 2005 by my colleagues at the university of Montana was that CBD exerts some of effects, on anxiety through a different receptor. The serotonin 1-A receptor, 5-HT1A. While that's been fascinating and very important, in fact, CBDA works on the same receptor, but it's a hundred times more potent! This leads me to believe that again, this could be leveraged as an antianxiety agent, but also in treating nausea with tiny doses that would just present no likelihood of any toxicity at all. That one has been looked at in animals, but no clinical trials in humans. So we got a lot of work to do yet.

**Lee:** And just to clarify, when we, speaking of the acid versions of the cannabinoids, even THC, these are all non-intoxicating?

**Russo:** That is true.

**Lee:** So why is THCA non-intoxicating and yet you get high from THC?

**Russo:** It just has to do with whether they bind to the CB-1 receptor which is the receptor in the brain that mediates intoxication in this instance. I never liked that word, but it, the CB-1 receptor is the target for getting high. And because neither THCA or CBDA lodge there with any affinity, they don't produce this kind of intoxication. To say that CB-1 is only responsible for intoxication hardly does justice to all its therapeutic effects. But all of this indicates to me the importance

of whole cannabis preparations because cannabis is like a drug store in one preparation. Its effects are really going to depend on the ratios of the various components. We see a lot of companies invested now in single components, what people call isolates, CBD isolates, THC isolates. These can be therapeutic, but to me they're really lacking in having the full attributes, that we can really achieve with a properly constituted cannabis preparation. THC on its own is a lousy drug. It's very hard to tolerate, it's very disorienting. Only with the addition of CBD that modulates those effects, or the terpenoids, that we really get an acceptable preparation that they can do a much better job.

**Lee:** So what about THCV and CVD V what is the stand for in these compounds and what are the implications? What do they do therapeutically? 'V' stands for varin, and this is just a way of saying chemically that there's a three carbon side chain instead of a five with THC and CBD. So THCV, usually seen in small amounts in cannabis from Southern Africa. You know, very small amounts. Recently it's been selective breeding to get much higher amounts of it. And it's a fascinating compound. Contrary to THC, which is a weak agonist at the CB-1 receptor, THCV is what's called a neutral antagonist. So it means it weakly inhibits that receptor.

When THCV is combined with THC, we hear experientially, from people who are using such a product, that the high is clearer and more manageable. We know that THCV, which has been tested in animals and humans has a lot of other

beneficial effects, particularly for those who may be obese, have the metabolic syndrome or type two diabetes, and it actually benefits the laboratory abnormalities of people with those kinds of problems as well as allaying hunger and leading to some reasonable degree of weight loss. But this is without the terrible side effects that we're seeing with some of the prior weight loss drugs. Those are different in their effects. They were what was called inverse agonists, an inverse agonist actually reduces the activity of the whole system.

So, it's knocking down the benefits of the whole endocannabinoid system. As many of us predicted years ago, that isn't a good thing and produces anxiety. Some pharmaceutical weight loss drugs can also lower seizure threshold making seizures more likely, and could increase the risk of cancer. Those kinds of drugs have dropped out of pharmaceutical research because of the side effects.

Rimonabant was a cannabinoid based diet pill as it were. That was what it was thought to be, but in retrospect, it highlights the dangers of a synthetic and very powerful inverse agonist. Not until it was on the market, did they really get stronger signals of these serious side effects. There were even couple of cases of de novo multiple sclerosis which developed in someone using this drug who had shown no signs of it before. So very scary stuff. This is another instance where it's clear that nature does it better.

Going back to THCV, that's not all. Basically, it has a number of other interesting properties, in contrast to Rimonabant, which could cause seizures, THCV is in the anticonvulsant. Additionally, it seems to have a strong effect on neuropathic pain, nerve based pain. That's a really strong therapeutic profile.

**Lee:** Last question, it's coming back to CBD, but the varin version of CBD, CBDV, what do we know about that? What is its potential?

**Russo:** Like CBD, CBDV, seems to have an anticonvulsant effect, benefit on seizures, but a different type. Whereas CBD works pretty well in general, CBDV seems particularly good for what are called focal seizures or seizures of partial onset that might be generated in one area of the brain. For instance, an area that's damaged after head injury. 'Really, it looks like the combination of the two, which we see in some chemovars of cannabis, might be a really good place to start for that kind of treatment.