Kratom as an Alternative for Opium Withdrawal: A Special Interview With Dr. Christopher McCurdy

By Dr. Joseph Mercola

JM: Dr. Joseph Mercola
CM: Dr. Christopher McCurdy

JM: Hi, this is Dr. Mercola, helping you take control of your health. Today we have the pleasure of being joined by Dr. Christopher McCurdy, who is a professor of medicinal chemistry at the University Of Florida College of Pharmacy. He also served as a National Institutes of Health (NIH) postdoctoral fellow in opioid biochemistry, which gives him particular expertise to expand on the topic of "kray-tom" or "kratom," as he will go into more details.

But this is such a big issue, because you may not be aware of this, but the No. 1 cause of death in the United States in people under 50 is from opioid addiction. This is a big deal. I'm so glad that we have Dr. McCurdy on to help us give us some practical alternatives. Welcome and thank you for joining us.

CM: Thank you for having me, Dr. Mercola. It's great to be here.

JM: Okay. I know one of your passions is to educate people about practical alternatives for this opioid addiction. Hopefully this platform will educate hundreds of thousands, if not millions, of people about this option. First, why don't you explain what "kray-tom" or "kratom" is and what the difference is in the pronunciation, because there are two different correct ways to pronounce it.

CM: Sure. I'll start off with the pronunciation, because there are actually more than a couple of ways to pronounce it. It just depends on who you talk to. If you're talking to someone in Thailand, Malaysia, Indonesia or Southeast Asia, where it's commonly used, you'll hear it called "kratom," "ketum" or "kray-tom." We like to pronounce it as "kratom," which is pretty close to how the Malaysians or the Thai, depending on who you speak to. [They] would recognize pretty much what you're speaking about. But I don't think there's really a wrong way to pronounce it. It's kind of like "to-may-toes" or "to-mah-toes." "Kray-tom," "kratom" – either way works.

JM: Okay. Great. What exactly is kratom?

CM: It's a plant. It's actually a tree. It's a tree that grows natively in the peninsula of Thailand and Malaysia. The peninsular part of Malaysia where it borders Thailand is where it's natively found. It does grow all over Southeast Asia in tropical areas.

It's interesting because it's a tree, but it's from the coffee family. It actually resides in the coffee family. Its family name is Rubiaceae, which is exactly what the coffee plant is in. Although, obviously, kratom, or Mitragyna speciosa, doesn't produce caffeine that we would think of, or the coffee beans. It produces some very different chemistries, which is what we're going to talk about, hopefully, today.

But it's been a traditional medicine that's been used in Thailand and Malaysia for centuries, primarily to improve the energy and the worker capability of the manual laborers, the outdoor laborers, in that area, who are working in fields, working in harsh heat and humidity conditions day in and day out. This helps give them more energy. But it's also used traditionally as a substitute for opium.

A lot of opium smokers who would run out of their opium would, in turn, utilize kratom preparations to sort of tide them over until they could get their opium. But they also found that it was a very good way to wean themselves off of opium or wean other family members or friends from opium.

They would use this brew as a tea, where they would pluck the leaves fresh in the morning, brew a tea, and then they would drink that tea throughout the day, either two or three times a day. It would be able to, at least, tide them over to opium again, or really get them off of opium altogether. Then they would move on to this. That brings about a lot of questions scientifically, as to why does that work, one; and two, is it habit-forming and habituating itself?

JM: Okay. Thank you for that explanation. You're actually a professor of medicinal chemistry.

CM: That's right.

JM: You've been studying this for close to 15 years, as I understand it.

CM: That's correct.

JM: Would it be fair to characterize you as one of the leading experts in the United States, if not the world, in this area?

CM: I would say that's probably fair. I don't like to toot my own horn, but I know that there haven't been too many researchers on the front end of this for as long as we have, at least for sure in the United States. There has been a group in Japan that has been working on this, prior to us starting in on it. But certainly we've been out long before even the DEA, the Drug Enforcement Agency, really knew what it was.

JM: Okay. I think perhaps part of the reason for that – maybe we can delve into this initially before we get into some of the therapeutic benefits – would be the inability to patent this, because it's been around for many years. Although they've just recently patented some of the derivatives of cannabis.

CM: Correct.

JM: I'm not sure how that differs in kratom. But maybe you can delve into it and discuss and enlighten us on one of the reasons that there's not a lot of research in this area and exploration to buy companies to bring it forward to the market.

CM: Sure. You can certainly patent a molecule or a process to obtain a molecule if you're going to synthesize or if you're going to create a new chemical entity, which wouldn't be the natural product. It could be a derivative of one of the natural products. Certainly, that would be patentable. But natural products themselves are not patentable any longer. It used to be in the past, but that that has been controlled, because natural products, according to the courts, belong to nature. They're not ours to profit from or really benefit from financially.

Now, health-wise, that's a different story, of course. But certainly, the patentability of the plant material or any molecule isolated from the plant material is not possible. Especially if you're looking at it for the types of uses. So not just the material itself, but also the uses. We couldn't just say we're going to patent the use of kratom for opioid withdrawal, pain treatment or anti-depressive treatment. All of those types of therapeutic potentials are even covered because of the historical use of it. There's really not much room there.

Now, if you were to produce any of the molecules through a patentable process, like a total synthesis or an enzymatic or biochemical synthesis, then that could be a product that could be patented. That process could be patented. That could move forward into commercialization. But simply just getting the plant material itself as it's available today in the marketplace and making an extract or doing something like that does not lend itself to a patentable standpoint.

JM: Thank you for explaining that. The reason I wanted to explore that is because this is such a significant issue, as I mentioned earlier, with the No.1 leading cause of death in adults in the United States below 50 is opioid overdose.

CM: Yeah. Overdose. Absolutely.

JM: Why don’t you address that and how Kratom can have a very significant role in this tragedy? We have more people dying every year than those who died in the Vietnam War from opioid.

CM: It’s sad. I mean, just a few months ago, we were talking about 91 persons per day dying from opioid overdose in the United States. That number, the most recent number now that's come out, is about 115 or 116 people a day now dying from opioid overdose.

JM: Sorry. Excuse me. Let me interrupt for a moment. It is the reason why the average life expectancy in the United States is decreasing. It’s because of this.

CM: Decreasing. Yes. It's sad. It's surpassed car accidents and other forms of death. Like you said, it's one of the leading causes, if not the leading cause, of death in the United States. It's a scary fact. This plant, I believe, has real potential to help curb this. It may not be the single solution to the crisis, but it certainly could help.

We could talk about the therapeutic aspects of the plant. In that regard, we've been doing a lot of work looking at how it affects opiate overdose and opiate addiction. But I think the bigger question here is making sure that we can have a product that can be in the marketplace that consumers can be confident and safe with and feel like this is something they can really use and trust. That's been

an issue lately, especially with some of the recalls that have been instituted. Most recently, because of salmonella contamination.

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JM: Okay. Before we get into some of the strategies that one can employ to avail themselves of this resource, perhaps you can describe how it impacts opioid detox or withdrawal and how it can mediate some of those symptoms, and go into the pharmacology and physiology, because you're an expert in that area.

CM: Sure, sure, sure. I'd be happy to. In fact, it's really fascinating. The plant has a number of alkaloids or what we would call nitrogen-containing compounds. Alkaloids are also what we would call morphine. Morphine's an alkaloid. It's an alkaloid of the poppy plant. Here in the kratom plant, we have what are called corynantheine alkaloids. Those are the more specific descriptions of compounds like mitragynine.

Mitragynine, or [mitragynine], which it's sometimes called, is the largest occurring alkaloid, the most abundant alkaloid in the plant, and thought to be responsible for most of its actions. When you see a compound in a high quantity in a plant, you usually correlate that to causing the behavioral or the pharmacological effects. There are many other alkaloids in the plant. Many of those compounds working together may cause beneficial effects and synergy from the plant material itself.

When you isolate out and look at just one compound or one of those alkaloids alone and look at its pharmacology, some of them are really fascinating. Mitragynine, in particular, is a very fascinating molecule in that it does have opioid activity. It was recently called out as opioid and many of the alkaloids were called out as opioids by the Food and Drug Administration (FDA) Commissioner. That's true. A lot of people were upset about that at first, but I think they need to understand that an opioid is any molecule that can interact with opioid receptors or those proteins in the body.

Opiates, on the other hand, are derived from the opium poppy. Those would constitute things like morphine, oxycodone or oxymorphone. Those types of drugs are referred to as opiates. But the opioid is really a generic term. Even our endogenous endorphins that bind, those are called opioids, not opiates. That's the one thing that has to be there.

For sure, mitragynine is an opioid. We've known that for a long, long time. Actually, I was kind of surprised when the FDA came out like that was big news, because that's been reported in the literature for some time, that these compounds and many of the compounds, the alkaloids in the plant, interact with opioid receptors. But what was surprising to me was why was this molecule so different than other opioid molecules?

We initially sent out purified alkaloid of mitragynine for a screen across a whole panel of central nervous system drug targets, so other receptors and proteins. What we found was a really remarkable profile of this molecule. For example, morphine, if you send it out and you look at it over various proteins in the brain, it really is pretty selective for opioid receptors.

Mitragynine binds with opioid receptors, so we weren't surprised to see that come back on the screen. But it also interacts with a couple of different serotonin receptors, dopamine receptors and adenosine receptors.

Adenosine receptors are actually the target for caffeine. It kind of maybe explains why some of these alkaloids in the plant might cause this excitation or stimulant-like effect. It also interacted with alpha-2 adrenergic receptors. Alpha-2 adrenergic receptors are many times used in opioid withdrawal. Agents that activate alpha-2 receptors, like clonidine, are used in opioid withdrawal treatment to stop a lot of the withdrawal symptoms of shaking, sweating, heart racing and this type of effect.

In all honesty, when I got the report back from the company that screened the molecules, I thought, "Wow. We just found nature's sort of answer to opiate addiction." Because here it was interacting with many of the same targets that we would target pharmacologically on an individual basis to get many of the same pharmacological effects out of it.

Then we went on to pursue much more detailed pharmacology studies, looking at what is it doing in the animals that we can habituate or make the animals addicted to morphine and then see how the animals behave when we start to take away their morphine and turn them over to accessing mitragynine.

What we saw was really remarkable. We compared mitragynine to methadone and buprenorphine, which are the two marketed drugs to treat opioid addiction and opioid withdrawal. What we found was a much cleaner profile. It wasn't incredibly superior to buprenorphine or methadone in the withdrawal treatments, but it seemed to be a little more milder.

It is activating opioid receptors. So does methadone and buprenorphine, but buprenorphine and methadone seem to be full agonists or activators of opioid receptors, whereas mitragynine, we think, is actually a partial agonist or a somewhat-activator.

I like to explain this, basically, as if you're going to turn a faucet on in your sink. A full agonist or a full activator would be when you turn that faucet all the way on full-blast, versus a partial activator, which would just turn that faucet on a little bit. You don't want as much pressure or as much output from that system. That's kind of what I compare those two. That's what mitragynine looks like. It looks like a partial agonist at opioid receptors, so it doesn't activate them as intensely as others. But also, it activates a different signaling pathway once the receptor is turned on, so to speak.

We used to think that only that was the event that happened. Some molecule interacted with a receptor, the receptor turned on and you got an output. Now, we understand that there are several signaling pathways that can be activated when that receptor is turned on.

It can be thought of as different inputs into a television or something like that, where the system's on but, hey, we're getting an input from a Blu-Ray player or we're getting input from a satellite – Just different ways of signaling. Mitragynine seems to signal in a way that seems to not cause

respiratory depression, at least to this extent that the other traditional opiate drugs do, like morphine, heroin and so on.

JM: That's the reason for the ultimate cause of death in most of these opiate overdoses. It's that the drug itself, one of its characteristics, is it suppresses the brain stem. You just lose the impulse or the signal to breathe.

CM: That's absolutely right. The respiratory depression or stopping breathing is essentially what is the cause of death from opiate overdose. Opioids are pretty safe to your body's organs, except for the fact that they are central nervous system (CNS)-depressants. They will shut everything off.

JM: As long as they don't stop you from breathing, it's okay.

CM: Yeah. Unfortunately, that's the endpoint. If it stops you from breathing, you're pretty much done. But I was talking to one of my colleagues, Edward Boyer, who's an MD-PhD at Harvard. He was fascinating, because he told me, "You know, if you've got to be addicted to a drug, opioids are probably the one that are the most okay to your body in general." But, yeah, you don't want to be addicted to any drug if you don't have to be. Of course it's not a choice. It's something that ends up developing from a disease state.

JM: Yes. Absolutely. This is not something people intentionally go for. It's not their goal at all. But it is so highly addictive. But it's an interesting observation. I've know it for a long time too, from my pharmacology courses. It's a very clean drug, as long as it doesn't stop you from breathing.

CM: Yeah.

JM: Can you expand on the different opioid receptors? The mu, delta and kappa and how mitragynine impacts that and its ability to help the withdrawal symptoms?

CM: Sure.

JM: As a therapeutic agent for getting people off of opioids.

CM: Yeah. There are what we think of as three traditional opioid receptors. Those were actually identified and proven to exist in the '90s, when the human genome project [started], that we could clone, and really when molecular biology moved forward to the point where we could really understand these things. But we do have three receptors. There's a mu opioid receptor, a delta opioid receptor and kappa opioid receptor, as you referred to.

Mu was actually named for its ability to interact with morphine. Morphine was named from Morpheus, the Greek god of dreams. Mu was designated as the Greek letter to interact with morphine. That receptor is really responsible for the euphoric effects that come with opioids. It's also very responsible for the respiratory depressive effects that are associated with opioids.

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All of the opioid receptors – I should back up before we talk specific about them. All of them are linked to numbing pain or dulling pain, or what we call analgesic receptors. They are able to block pain signal transmissions or slow pain signal transmissions down at the spinal cord level, so that the brain doesn't feel or process the pain as much. All of them are good in terms of trying to target as a pain reliever pathway. Of course it's the best pain reliever pathway we've been able to identify up to this point. Really, mu is the focus. The mu opioid receptors is the focus of a lot of those activities.

The delta receptor, for a long time, was thought to be also a great target for selective analgesics. In fact, there was a whole company called Delta Pharmaceuticals that started out really thinking they could produce a painkiller that had no addictive liabilities to it. The delta receptor looked very promising. In fact, it doesn't seem to have the addictive capabilities associated with it, or at least not as strongly as the mu receptor does.

Unfortunately, the delta receptor seems to be linked to convulsions, as one of the outcomes. Many of the drugs that were being tested and studied in trying to develop this delta-selective opioid receptor ligands were halted due to seizures in many of the animals that they couldn't resolve. Delta kind of was abandoned for a while. But we also know that mitragynine in the kratom plant, many of these compounds don't seem to interact with delta receptors, or at least we can't measure them interacting with delta receptors with our current technology.

When we move on to the kappa opioid receptor, the kappa opioid receptor seems to be sort of the yin and the yang to the mu receptor, in that instead of causing euphoria, it seems to cause dysphoria, or a bad feeling or aversive-type feelings. Again, very good target for killing pain.

I think what's interesting is they thought that they had discovered, in the ‘70s and ‘80s, they thought they discovered a selective kappa opioid non-addictive painkiller that was just as potent as morphine, if not more potent. They moved into human clinical trials. The people who took the drug said, “I don't know what that was, but don't ever give it to me again,” because they felt so awful and bad they dropped out of the trials even after a single dose. There is this aversive effect that comes with a kappa activation of the kappa opioid receptor.

There's sort of this whole balance. There's analgesia associated with all three receptors. One has a really euphoric feeling. That's the mu. Delta, we’re not really sure. [It’s] probably the least understood of the three, but, again, good analgesic target. And then the kappa, also an analgesic target, but seems to cause that reversed – instead of euphoria – dysphoric behavior.

JM: Is kratom an agonist or partial agonist for all of those receptors?

CM: We think it's a partial agonist for all of the receptors. It seems to be very weak at delta and kappa. What’s interesting is you can't really estimate. As I said, you can't really measure interaction with the delta receptor. But in animal studies, you can actually block some of the effects of mitragynine or kratom with delta receptor-selective antagonists or blockers for the delta receptors. Delta system seems to be involved somehow. We just don't really know all the pieces of the puzzle yet to figure that out.

JM: Okay. Is it activation of the mu opioid receptors that likely contributes to the significant addictive potential of opiates? Does kratom have a significant stimulus? Which kratom is a stimulus to this relative to the addictive potential?

CM: Right. It's interesting. We have a paper that's under review right now in addiction biology with a colleague of mine, Scott Hemby, from High Point University in North Carolina. Scott and I got together and started thinking that we could look at what is the actual abuse potential of mitragynine. He trained rats to self-administer morphine. They were able to learn to press a lever and they would get injections of morphine. If they press the lever a number of times, they would get an injection. We were able to look at that.

Once you trained those animals, you can then substitute that morphine for some other drug and see if they think it's like morphine, right? We substituted mitragynine and they stopped self-administering. It seemed like, "Well, this is interesting. Maybe it doesn't activate the mu opioid receptor in an addictive manner or in a manner that would produce addiction." Of course we did it at only one dose. We did it at only a limited fashion at the moment, because we're hoping to get some grant funding to really pursue this.

But the fact of the matter is many drugs will substitute for morphine – many other compounds, like oxycodone or oxymorphone, that we know are used clinically. But mitragynine did not substitute. What was even more interesting is we couldn't train over several doses. We couldn't train the animals to self-administer mitragynine to themselves. This was a completely – Well, for us, it was a very strong indicator that mitragynine doesn't have an abuse potential. In fact, that's kind of the sort of story of our paper.

Now, that's not the whole story of the plant. There are other molecules in the plant, mitragynine being the major one. Of course, like I said, it doesn't seem to activate the opioid receptors as fully as other things. But there is another compound: the 7-hydroxymitragynine, which is an oxidative byproduct, we think, from the drying of the leaves.

We've actually been doing a lot of studies in the last month or two on fresh extracts from Malaysia. We're not seeing 7-hydroxy present in the fresh extracts. We've also been trying to figure out how does that process take place.

It could be various things. I mean it could be that it is an oxidative byproduct, or it could be that it's actually because most of the material that's coming into the United States is actually coming from Indonesia, which is a different growing region, different climate to some extent, and, for sure, different microclimates. There could be different bugs present. There could be different soils, of course. [There are] many different variables that we don't understand yet either.

But the 7-hydroxymitragynine, which is known to be, in very small amounts – if it exists at all – a full opioid agonist. It's a very potent opioid agonist. It has a very fast-acting opioid full-agonist from what we can see. That molecule does substitute directly for morphine. It also can be habit-forming.

I think what's even more interesting about this recent study that we did, we treated animals with mitragynine that were already addicted to morphine, and then re-exposed them to morphine self-administration. They could then go ahead and work again for morphine. It decreased their intake of morphine. This was pretty exciting, because it also shows that there's some maybe therapeutic potential in reducing opioid intake.

That begs the question about if there is 7-hydroxy present in a very small amount, and you have maybe 20 times or more of mitragynine relative to the 7-hydroxy. Is that actually counteracting the effect of the 7-hydroxy compound so it's not as bad? It's really hard to say at this point, because we don't have all the science done. We've got lots of additional studies planned and hope that we can figure out what's going on there.

But our take home is that kratom, as a whole, is pretty much on the addictive level of coffee. It's really not that harsh of an addictive plant, but it depends. It's starting to look like it may depend on what level of this 7-hydroxymitragynine is present in the material or in the product that's utilized.

JM: It brings up an interesting question. It's a very intriguing observation that you may have 7-hydroxymitragynine. But it seems to be present in the plant as a result of the oxidative stresses from drying the leave.

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It would suggest that taking the fresh plant and making the tea or the extract would almost eliminate this metabolite or this oxidative metabolite, and essentially eliminate their addictive potential. Would that be fair to say?

CM: Yeah. That's our hypothesis right now. I think it's fair to say that at this point. We've been fortunate to really gain some good collaborations with the University of Science in Malaysia, where they have actual, I would say, cultivars of Mitragyna speciosa trees that they can use and study as well. We've been really excited because we're getting fresh extract material from them.

We're also looking at some of the traditional preparations that are made by traditional users of this in Malaysia, where they're going out to their own tree in their own backyard picking the leaves fresh, brewing the tea in the morning. We're getting samples of some of that to analyze and test.

But so far, everything that we've looked at with fresh material – We've looked at several locations, several different farms around Malaysia that that we've been able to get access to. We don't see the 7-hydroxy there, which then leads me to believe that there's only two things that can be going on. One is it is this oxidative process that's causing either drying out of the leaves or the sun or the heat – excuse me – any of those things that could be creating that.

The other is the environmental factors. It could be an environmental pressure factor that you see in Indonesia that you don't see in Malaysia. That could be a number of things: bugs and soil type. Many, many factors could be involved there.

But, yeah, I think if we can get fresh materials, particularly that from those places that we've tested in Malaysia, you can eliminate that 7-hydroxy and then potentially eliminate the abuse liability.

That's one thing that we've been very interested in from the start, because I have had this hypothesis based on the three-dimensional structure differences between mitragynine and 7-hydroxymitragynine.

If we were to model those structures, 7-hydroxymitragynine looks much more like morphine structure when it's in three dimensions. That's just placing several elements that we know are important for recognition of a molecule at an opioid receptor in that same alignment, versus mitragynine that looks very different from morphine structure in three dimensions. I then long hypothesize that the 7-hydroxy was going to be a problem as we moved forward. As we've seen the research come forward, we've started to really realize that is the case.

The exciting part of it though is, yes, 7-hydroxy is potent. It's probably a very addictive molecule, but it also seems to be a safer molecule than the traditional opioids, like morphine and the derivatives of morphine, in that it doesn't seem to cause the respiratory depression. Again, lots of things to deal with here, lots of questions to still answer.

JM: Okay. We really sort of skipped over the use of kratom as a treatment modality for opioid addiction. Relief of the opioid withdrawal, as I understand from watching a previous interview with you, that the only thing that it doesn't do, at least the whole plant extract, is the shaking or wet-shaking dog syndrome.

CM: Wet dog shaking. We measure opioid withdrawal in a variety of fashions. But what you really have to look for are behaviors that wouldn’t be exhibited in a normal healthy animal. What we look at are actually, one, which is just locomotor activity, the way that the animal moves around, freely moves around. Two is paw tremors. If they're shaking, their paws are normal. A mouse wouldn't do that. We look at jumping behavior. Really, what we're looking for is an increase in jumping behavior because mice, just normal mice, will jump anywhere from one to two times in about a 30-minute period if you're observing them.

The other thing that is totally not usual for a mouse is to do a wet dog shake, or what we characterize as a wet dog shake. That's literally just like what it sounds. It’s from the head to the tail. They will stop and shake from the head to the tail. We think that's a serotonergic effect, so related to the serotonin receptor systems. But it's something that we see. If we give an animal – One last thing. Teeth chattering is another thing that we can measure. We can hear these mice and their teeth chattering, which they normally don't do either, even if they're cold, unlike humans.

Those are different measurements we can look at. We also look at body weight. All of those effects were eliminated when you compare it to just precipitated withdrawal. What we did was we habituated mice to morphine over five days, with escalating doses of morphine on each day. They got morphine doses twice a day for five days in a row. They started out with a low dose. Every day, the dose doubled.

On the final day, the sixth day, they received a dose in the morning, and then about fifteen to thirty minutes later, they receive a dose of naloxone, which is the reversal Narcan, the reversal agent of opioid overdose or opioid treatments. What that does is it knocks all the opioid agonists off of the opioid receptors and sort of shuts off that faucet from running.

JM: It knocks off all of the receptors in mu, delta and kappa?

CM: It does. It's more selective for mu, but it's not a mu-selective agent.

JM: Okay.

CM: So it does work on all three. We call it kind of a pan-opioid antagonist. But it does have more preference for the mu opioid receptor. Most of our agents that we're talking about are interacting, really, at that receptor, that we'd be worried about someone overdosing on anyway.

But to just go on further, the withdrawal symptoms – See, we can see all of those things. If you just precipitate withdrawal in a mouse, you'll see that teeth chattering, paw shaking and wet dog shakes, all these different behaviors I just mentioned. That's our baseline. That's what we measure. And then we're looking at drugs like buprenorphine, methadone or, in this case, kratom, to see how it can lessen those effects over time.

As I mentioned before, we compared buprenorphine and methadone. It did better than both of those in all the measures, but it wasn't incredibly, incredibly superior, but it seems to be safer. Methadone has been known to cause a lot of overdose deaths because of its very narrow therapeutic window and very long, long half-life, so it stays in the body for a very long time. It takes a long time to activate as well.

But when we gave kratom tea – We would brew kratom tea just like someone would in Asia. And then we take that kratom tea and we lyophilize it or freeze-dry it. And then we analyze that through our colleague, Dr. Bonnie Avery, who's our analytical guru and chemistry guru on that side. She can tell us what the content of the alkaloids are in that particular amount. We can normalize the doses for the animals based on that.

We give them doses of the lyophilized tea by mouth, and then we precipitate the withdrawal again five days later. We do five days on morphine, five days on the kratom, where they were getting kratom twice a day, and then we precipitated again on the last day of that.

But we also did animals that had never had morphine. We just exposed them to kratom for five days twice a day, and then we precipitated withdrawal in those animals with naloxone. In both cases, whether they were exposed to morphine, switched over to kratom, or they were just on kratom by itself, they all experienced only this wet dog shake as a side effect. We went back to see if we could even eliminate that.

Interestingly enough, just anecdotally hearing human reports of getting off of kratom, you hear about runny noses, sometimes a little bit of irritability or shakiness, or just a malaise feeling, a down feeling overall. A lot of that could be attributed to serotonin-like system activation, which would somewhat be analogous to this wet dog shake in the mice.

Now, I can't say that, definitively, it's the same thing. But we can draw that sort of conclusion or speculation that they're somewhat related. We were interested to see if we could eliminate all side

effects altogether. So we went in and we performed some manipulation on the lyophilized tea to remove certain alkaloids and certain chemicals. What we found was we could eliminate all the side effects with a tea preparation that's been modified.

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In reality, that would be a patentable system, because we could generate a potentially therapeutic option that has been manipulated. Not genetically modified organisms (GMO) or anything like that. We've essentially gone through and decaffeinated it, like you would decaffeinate coffee. But we've removed more than just one thing from that plant mixture and gone back in and seen that it works with no side effects on withdrawal. That's very similar to just pure mitragynine in itself.

If you take mitragynine out and purify it, and then do the same type of paradigm I'm talking about, where we look at whether the animals have a withdrawal symptom from mitragynine, they do not. It's a very, I think, very fascinating promising molecule. I think the molecule itself would rival methadone or buprenorphine in the pharmaceutical industry. But the problem is you will go back to what we started out talking about patentability and being able to get some sort of income revenue back to pay back all the investment made in bringing something like that to the market.

JM: But it sounds like it's possible. I mean you've got a patentable process.

CM: It's possible.

JM: There's certainly a need for it.

CM: Absolutely.

JM: Hopefully. There's no interest in any drug developers to do this, though?

CM: Not that we've seen. The reason is – and then let me be clear – they are interested in the modified formulation. The problem that we're facing right now, which we're hopefully going to be able to overcome soon, is verifying our biomass source.

Verifying where our plant material is coming from and if that plant material would live up to the standards that the FDA would require in order to ensure public safety. Can we have a legitimate verified source that we can trust that we know hasn't been treated with pesticides that could be dangerous to humans, hasn't been treated with heavy metals-containing waters or fertilizers?

You know, basically, if it's a clean, good product that we can get on a regular basis and be able to standardize, that would be the next thing, because you don't want to have the product being really good one day and not so good the other day because the alkaloid content has changed from one batch to the other. You have to have batch-to-batch consistency. You have to have this sort of provenness in biomass.

Now, that's existing in our current culture. I mean, every day, people who have smoked Marlboro cigarettes will go buy a pack of Marlboro and it tastes exactly as it did 20 years ago. They'll stick to that brand loyalty. That's because they have figured out a great way to blend these products so

that there's a consistent product day in and day out. Same thing with teas. Same thing with coffees that we become attached to in the flavor profile. I think it's very possible to do if we kind of learn from those industries moving forward.

JM: Well, part of that is that they're growing the product domestically. That's one of my burning questions. Is this plant indigenous to Southwest Asia and Indonesia? Can it be grown in the USA? Can it be grown in Florida? It would seem like you should be able to. If you can do that, you should be able to provide a very consistent raw material, which would satisfy the requirements.

CM: We actually have been contacted by some individuals who are growing kratom trees in South Florida. It appears that they're doing very well and that they could survive. They're interesting. I have a student here right now from Malaysia who says Gainesville is probably too cold to grow the tree. But as you move down towards Miami and really the tip of Florida, it's probably a good enough zone and climate to be able to grow the tree.

I have seen pictures from two different individuals who are growing trees. Some of them even have trees that I would say are maybe 15 to 20 feet tall with a good age to them. It looks like they can survive in Florida environment.

JM: Interesting. That's great.

CM: We're also working with horticulturists at the University of Florida to try to understand what conditions the plants need to thrive in the United States, particularly, of course, in Florida. But can they be grown in a greenhouse? What types of nutrients do they need? How well are they going to survive?

One thing we know in Florida is that the orange crop is in a little bit of danger due to greening. Maybe "a little bit" is an understatement. But many orange growers are looking for alternative crops. One of them happens to be cannabis in the state. It's really for hemp, not for the medical marijuana, but for the hemp product. There is actually an article in The Gainesville Sun today about that, and the University of Florida's (UF) involved in really testing these products to make sure they don't have enough THC in them to be hemp.

There are some alternative crops in that way. But we've also been approached by some growers, commercial growers, for interest in what the real feasibility would be to grow Mitragyna speciosa or kratom trees.

I think there's an interest in it. It may be a groundswell of interest to really see if we can create a new type of product for these growers to look at. That product would ensure us as researchers or producers of a pharmaceutical that we would have a good reliable source that we can control and understand.

We could then hopefully blend up and produce a really top-notch product that we can do some really controlled clinical trials with, and then also move that on to helping people. That's the whole goal here. It's to move it over so we can really get help to a lot of these opiate addicts and hopefully get them off.

JM: Sure. We've got tens of thousands of people dying every year, hundreds every day. I'm wondering if you could briefly discuss the legal status. I know there was an effort, I believe, last year by the DEA to categorize it as a Class 1 controlled substance. That was overturned, which was unusual for the DEA, but I believe it's legal in all states. I'm sure you can expand greatly on that.

CM: It's not legal in all states. It's legal in most of the states. There are a few states where it is illegal, including Alabama and, I believe, Louisiana. Illinois has an area that's illegal. In fact, the last time I checked, I think it was six or seven states [that] have laws on the books, including Florida. It is banned in one county in Florida.

JM: In Orange County?

CM: I don't want to say for sure. I think it's Brevard, but I really don't know. Or Broward. I'm not sure.

JM: Yeah.

CM: In the West Palm Beach area, I believe. But it's fascinating because kratom ended up being a product of the wrong place at the wrong time. What I mean by that is it was also available in gas stations and in head shops the same time that spice and bath salts were available.

In a haste to put legislation out banning bath salts and synthetic marijuana spice – I believe those really do need to be in Schedule 1, especially many of those compounds haven't even been tested in humans until they were into the marketplace to go into humans, let alone even tested in rodents. I mean many of them never saw a living system until they were putting it out into the marketplace for people, so that's scary.

But kratom was there on the shelves right in line with all of that. Then the next thing, there were the five-hour energies, the Stackers and all the caffeine products that are there. Kratom was sort of the oddball out. It ended up getting lumped into a lot of states' – with synthetic cannabinoids and bath salts – bills. It's the only natural product that's listed in some of those. It's why it's outlawed in those places.

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But as far as on the federal level, they know it's completely legal up to this point. The DEA did come out in the fall of 2016 and suggested that they were going to put 7-hydroxymitragynine and Mitragyna speciosa, or kratom, into Schedule 1 of the Controlled Substances Act. Schedule 1 means absolutely no medical use. It means it's a highly addictive substance and will essentially halt research on it.

Marijuana is in Schedule 1, as is lysergic acid diethylamide (LSD), as are many other drugs that are actually starting to be studied for medical potential now. We could do another whole hour on other psychoactive substances, I'm sure. But they essentially wanted to put this into Schedule 1, saying that it has absolutely no medical use. But there's no science out there to back up that

rationale. The DEA was contacted by several entities and many researchers. Many researchers contacted Congress to get congressional intervention.

Suffice to say, there were many points of pressure on to the DEA to not make this scheduling official. The DEA decided to open up a 30-day comment period to obtain information. Every one of those scientists, consumers and people who have benefited from it flooded the DEA with messages. They received over 23,000 individual messages at the DEA in that 30-day period to keep this thing out of Schedule 1. It worked. [It was] very unprecedented. Just like you said, this doesn't happen.

The DEA decided to withdraw its intent to put it into Schedule 1, but they have that threat there, that at any moment in time, they could certainly pull the trigger and make it illegal. We had actually shut down our research while that threat was undergoing, because I didn't want to wake up one morning, come into work and be in violation of federal law at the university. I don't have a Schedule 1 research license.

We had packed up all of our materials and sent it to our good collaborators. Scott Hemby at High Point University does have a Schedule 1 license. Scott held on to the material for us for a while. I finally started getting just too antsy waiting around doing nothing in the face of all this crisis. We said, “Scott, we need our stuff back so we can get back to work and get the machines going again.” That's exactly what we've done.

We've really cranked up and intensified the work to gain more science, get more science out there, and, hopefully, be able to get some human science, really controlled human science, performed at some point. Because everything that's out there in the literature or in stories – I have emails and emails and emails from people, thousands of emails, suggesting how helpful kratom has been to them in their life. Those are all fantastic stories. I love each and every one of them. I read them all. I don't respond to every one, but I read them all. It's encouraging to me.

The problem is none of those are scientifically valid in what we would call a science sense, because they haven't been done in any controlled trial. We haven't really validated anything. They all just are suggestive or what we call anecdotal evidence that this is working. But, heck, when you have –

JM: But you have case reports.

CM: Yeah. When you have hundreds of years of known safe use of this product in Malaysia and Thailand, and then you have an estimated somewhere between 4 and 7 million Americans who are using kratom on a daily basis. That's based off of internet sales.

JM: Yeah. Perhaps you can touch on the safety of kratom, because I believe there's been some deaths associated with it, but they all appear to be with other drugs. People were using it with other drugs. But its safety profile seems to be profoundly effective.

CM: The safety profile is remarkable. Yes, there have been some deaths associated with kratom. Most of those have been in combinations with other drugs. There are a couple of cases that have reported only finding kratom or mitragynine alkaloids on board the toxicology reports.

But it's almost impossible to understand based on – We just don't know enough about how it's being metabolized, what's going on. If somebody has some impaired function, they may be on a high-protein diet or they may be on some other type of diet that they think is healthy, but unfortunately isn't healthy when taking kratom. We don't know the answers to all of these questions. There's a lot more work that has to be done.

However, I will go back and say that, again, in the indigenous population where this is used, in Malaysia and in Thailand, there haven't been any reports in the history associated to only kratom. In fact, it's never been a drug of abuse or a drug that's sought out for pleasure. It's a societal norm. It's just like [what] coffee is in the United States.

I mean these people drink this in the morning before they go to work. They drink it in the mid-afternoon. They drink it in the evenings. Many of the men will gather. They don't drink alcohol, most of them. But many of the men will gather in the evenings and drink a glass or two of kratom tea as they socialize. It's a very societal cultural custom that's known there. It's been safe for hundreds and hundreds of years.

In the U.S., it's been fairly safe albeit – Any death is a sad, sad event. We don't like to see it. But we need to understand what's going on and how it's happening, even in the few cases that have been reported. We need to understand. Is it a combination with antidepressants that's a problem? Is it a combination with other drugs, like muscle relaxants? We just don't know enough of these answers yet to really tell people how to safely use the product, although millions of consumers are using it and appear to be using it safely.

The other issue on safety is it comes back to that thing I talked about earlier in terms of getting a reliable source of the biomass and really understanding where the products are coming from. I've heard rumors that some products have been shipped into the United States under the form of kelp, so just as seaweed. It comes in wet and damp. That could be some of the problems that we're seeing now with the salmonella outbreak that has been tied back to kratom.

JM: It's the mycotoxin.

CM: Yeah. There are issues. The material that's coming into the United States isn't always screened to [ensure] it's good and safe for the consumer. There are some companies that are screening it for everything that the FDA would require from a botanical product. They're screening for fungus, bacteria, mold and pesticides – all those things we talked a little bit about before. But then there are companies that aren't doing that and are just putting products out. I can't even tell you which products are doing it or not.

JM: I know you can't. And even if you could, there's no assurance that that company wouldn't change their process the next day.

CM: Absolutely.

JM: I'm wondering, especially with millions using it and the tens of thousands who need it, otherwise they're going to be dead, if there is any process that you could recommend and strategy that an interested consumer could follow to increase the likelihood that they're getting a reliable consistent product right.

CM: Right. I wish there was a way we could do something like – I envision a product that's available for other things, something called like "Kratom Safe," right? So you actually know that what you bought, you could take a capsule and put it into a vial of liquid, and if it turned into this color, you knew you wouldn't want to drink or eat it. But, unfortunately, there isn't. There really isn't any way to tell at this point in time what is and what isn't safe.

One thing that we have high hopes for – I won't say this will happen, but we really like to see the United States Pharmacopoeia (USP) develop a monograph for Mitragyna speciosa, which would be a standardization product. And then if you could earn a product that could get the U.S. Pharmaceutical Corporation (USPCO), which we see on many vitamin products.

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By the way, the USP is developing – I'm a member of this as well, a voting member. They actually are developing a monograph on cannabis right now. It can be done. I really would like to see this developed. That would, again –

JM: It would solve the problem.

CM: It would solve the problem and give the consumer assurance that they're getting a quality material. I really wish that we were five or 10 years in the future where we had all these growing conditions figured out in Florida and a product we could trust.

JM: Yeah. At least we have something to anticipate. But getting into specifics now, there are three different strains or variety of different strains of mitragynine or kratom. I'm wondering if you could briefly touch on that. And then I want to go on about preparation too. There's oral versus different types of extracts.

CM: Sure. Just real quick. The different products – there's a red vein, a white vein, a green vein, and then there's one called "Maeng Da." Those are all different. The green and white vein are actually considered the same. It just depends on when the plant is harvested as to if the vein is green or white. The red vein is different. Many claim that the red vein is more potent, has more of the alkaloids in it. But what we've been learning – and we've harvested all of these different products from these different locations in Malaysia – is it's not so much about the strain itself. It's about where the product is grown and what the potency is in there.

We've analyzed many products that are available in the marketplace through ultra-high performance liquid chromatography and mass spectrometry. What we've learned from that is sometimes the ones that people think, the red vein being the strongest, actually have the lowest content and material in them compared to the other products that are actually cheaper.

But, again, it's one of these things where there are no real labeling laws. There's no consistency. There's no idea. You could buy the red vein one day, buy it the next week and it's less potent. Go back in the next week and the potency's back up. [We] just don't really know where these things are. But from what we've seen in the natural environments, the difference is really going to be where these microclimates are producing the materials.

If we get back to the Maeng Da strain, which is touted as being one of the sort of high-end and superior strains, that actually comes from a horn-shaped leaf. They call these tooth leaves. They actually have – I wouldn't go as far as to say they look like oak leaves, but they definitely [do]. Instead of a nice smooth leaf, like what you would see on mitragyna leaf, you see it's smooth at the bottom and then real jagged edges up to a point. Again, we haven't seen a huge difference in any of these supposed strains. A lot of it comes down to marketing, and what can play to the consumer environment.

JM: Thank you for expanding on that. The important question is – Traditionally, kratom has been used as a water extract and the tea from the leaves. I don't know if kratom grows into flowers, berries or other materials of that, or even the inner bark. I'm wondering if you've looked at those extracts or even looked at ethanol extracts, where you're getting different alkaloids out.

CM: Yes. We did a systematic study with different solvents. We've done ethanol, methanol and acetone. There's a handful of different solvents that we've looked at in terms of extracting and trying to maximize what we're pulling out of the plant material, because the aqueous extract, the water extract is only going to pull out a certain amount of material. Methanol is usually one of the greatest ones to pull out just about everything from the plant. It's sort of the universal solvent. It pulls many of the materials out.

We've even studied those extracts in the animals. We've looked at differences between being able to pull out all the materials, or just an aqueous extract or whatnot. There are differences. There are definitely differences if you purify a molecule and take it outside of that extract, because it seems very clear that many of the compounds and alkaloids within the plant material work somehow in synergy with each other to help either absorb those molecules into the body system or keep certain ones out of the body system.

It's really fascinating how these plants do that and help to gain access to what the therapeutic compounds are, the ones that can get in for benefit from those plant materials. We've looked at many different extraction products. We've also looked at different extracts so you can get alkaloid-rich extracts, if you get rid of many of the other materials from them. But we do a lot of that just on an everyday basis. I'm sorry. You said something else other than –

JM: Well, the extracts of the leaves. That's the traditional ones they were using. Did you look at the other materials?

CM: Oh, the bark and the flowers.

JM: And the flowers or the berries or if it makes a fruit even.

CM: I got you. It does fruit. The fruit is produced in a flower form. Of course, if you search on the internet, you can find pictures of this flower. It's a yellow pod that, eventually, when those flowers drop, those are where the seeds are. The seeds are very fragile. They are not very viable for a long period of time. It's not something that you could collect seeds and then hope to grow from seed. Most of the trees have to be propagated from cuttings. Excuse me. It makes it difficult, unless it's in the indigenous environment where it can naturally grow.

But we have looked at flowers. We have looked at bark. We've looked at stems. We've looked at roots. We've essentially taken the entire tree and grounded it up and looked at various places. There are reports from the users in Indonesia that they actually will pick the leaves off the tree. They'll remove the vein completely, because they say the vein is too bitter and too strong. They'll remove the vein and use only the leaf material.

We do know that there's a higher concentration of the alkaloids in the vein than there is in the flesh of the leaf material. Most of the products that we see coming into the U.S. are whole leaf, just chopped up or ground up, so they do have the vein. They do have all of that.

One other thing that I find really fascinating is the bark or the branches. If people feel like they need a boost, they will put the bark branches into their teas as they brew it. They say it makes it much stronger. We really haven't found out what that molecule is that's helping to make it stronger yet. It could just be one of those sort of urban legends or the old wives' tale that's been handed down over the years. But we haven't seen much of a difference outside of the leaves.

There are different compounds, of course. There are different compounds that are in higher quantities in the stems, in the fruits. We're trying to pursue and see what the pharmacology is that's associated to them. We went for the – no pun intended – low-hanging fruit first, which was the major alkaloid of mitragynine.

JM: Is there a difference for those who purchase and the millions that are using it if they swallow it, the ground-up leaves, versus brewing it as a tea? Do we absorb similar amounts of the alkaloids?

CM: I think you'll probably get similar amounts. We haven't looked at that specifically. We haven't compared animals with freeze-dried tea and ground-up capsule material, where we just actually have them swallow a capsule fully. We haven't done that direct head-to-head comparison. But I would assume that once it dissolves out of the capsule and gets into the stomach acid, it's going to get extracted fairly well, like it would do in a water environment.

Most of the time that people brewed teas from the leaf material, they'll also add citric acid, lemon juice or orange juice to the water to make it more acidic and pull more of those compounds out. I think, in theory, it should be a very similar process to the water extract.

JM: Okay.

CM: But the water extract will concentrate it better.

JM: Alright. You've been an enormous wealth of information. You hold the keys to really an antidote for a perplexing problem that is killing tens of thousands of Americans every year needlessly. There's a safe natural solution. I really applaud your efforts and your work to bring this forward.

CM: Thank you. It's a whole bunch of us. It's not just me.

JM: Yeah. You're surely one of the leaders. I appreciate your efforts.

CM: Well, thank you.

[END]