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Kratom as an Alternative for Opium Withdrawal

Analysis by Dr. Joseph Mercola ✔ Fact Checked | June 02, 2023

STORY AT-A-GLANCE

- Opioid overdose is the No. 1 cause of death of Americans under the age of 50, and opioid addiction is so widespread it has led to a decline in the average life expectancy in the U.S.
- Kratom has been used as a traditional medicine in Thailand and Malaysia for centuries, primarily to boost energy. It also has a long history of use as an opium substitute and to wean off opium
- Kratom contains corynantheine alkaloids such as mitragynine, which interacts with opioid receptors, adrenergic receptors, serotonin receptors, dopamine receptors and adenosine receptors
- While the alkaloids in kratom bind to opioid receptors, animal trials suggest the abuse potential of kratom is very low
- A compound found in dried kratom leaves, 7-hydroxymitragynine is known to be a fast-acting full opioid agonist that substitutes directly for morphine and can be habit-forming. This compound does not appear to be present in detectable amounts in fresh extracts, so using tea from fresh leaves and/or extracts may be a way to circumvent its addiction potential

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With opioid overdose being the No. 1 cause of death of Americans under the age of 50, it's quite clear we need safer alternatives to pain management. Rampant opioid

addiction is so significant it has even led to a decline in life expectancy in the U.S.

In this interview, Christopher McCurdy, professor of medicinal chemistry at the University of Florida College of Pharmacy and former postdoctoral fellow in opioid chemistry at the University of Minnesota under a National Institutes of Health (NIH) postdoctoral training fellowship, discusses the use of kratom for pain relief and opioid withdrawal.

He's one of just a handful of American scientists studying kratom, which he's been investigating for nearly 15 years. According to McCurdy:

> *"[A]bout 115 or 116 people a day [are] now dying from opioid overdose … It's surpassed car accidents and other forms of death … 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."*

What Is Kratom?

Kratom (mitragyna speciosa) is a native tree of Thailand and Malaysia, but it grows all over Southeast Asia in tropical areas. While part of the coffee family, it has a very different chemistry than coffee beans. Kratom has been used in traditional medicine in Thailand and Malaysia for centuries, primarily to boost energy. It also has a long history of use as an opium substitute.

> *"A lot of opium smokers who would run out of opium would use kratom preparations to tide them over until they could get their opium. 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,"* McCurdy says.

> *"They would … pluck the leaves fresh in the morning, brew a tea and then drink that tea two or three times a day … That brings about a lot of questions scientifically, as to why does that work, and is it habit-forming and habituating itself?"*

Unfortunately, there's not much research being done on kratom, in part because you cannot patent natural products such as plant material. You also cannot patent the plant's use for opioid withdrawal or pain relief of antidepressive treatment, as all of these therapeutic potentials are covered under the historical use of kratom. McCurdy explains:

> *"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 getting the plant material itself as it's available today in the marketplace and making an extract … does not lend itself to a patentable standpoint …"*

Kratom Has Opioid Activity

McCurdy has studied how kratom affects opiate addiction and withdrawal. The plant contains a number of alkaloids (nitrogen-containing compounds). Morphine is an example of an alkaloid found in the poppy plant. Kratom contains corynantheine alkaloids, the primary one being mitragynine, thought to be responsible for most of its pharmacological effects. That said, there are many other alkaloids in the plant, and many of its compounds work synergistically to cause beneficial effects.

Mitragynine does have opioid activity. It and many other alkaloids in the kratom plant were recently called out as opioids by the Food and Drug Administration (FDA) commissioner. "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," McCurdy says.

In other words, an opioid is not identical to an opiate, derived from **opium poppy**, such as morphine, oxycodone or oxymorphone. Opioid is a generic term that include even endogenous endorphins that bind to opioid receptors in your body.

Mitragynine Is Different From Other Opioids

While it has opioid activity, the mitragynine molecule is different from other opioid molecules. McCurdy explains:

> *"We initially sent out purified alkaloid of mitragynine for a screen across a whole panel of central nervous system drug targets … What we found was a really remarkable profile of this molecule. For example, morphine … is pretty selective for opioid receptors. Mitragynine binds with opioid receptors … but it also interacts with adrenergic receptors, serotonin receptors, dopamine receptors, and adenosine receptors.*
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> *Adenosine receptors are the target for caffeine. It kind of explains why some of these alkaloids in the plant might cause this excitation or stimulant-like effect. It also interacts with alpha-2 adrenergic receptors, [which] are … used in opioid withdrawal. Agents that activate alpha-2 receptors, like clonidine, are used in opioid withdrawal treatment to stop withdrawal symptoms such as shaking, sweating and heart racing …*
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> *In all honesty, when I got the report back from the company that screened the molecule, I thought, 'Wow. We just found nature's answer to opiate addiction,' because here it was interacting with many of the same targets that we would target pharmacologically on an individual basis …*
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> *Then we went on to pursue much more detailed pharmacology studies, looking at what is it doing in animals addicted to morphine and how the animals behave when we take away their morphine and turn them over to mitragynine.*
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> *What we saw was really remarkable. We compared mitragynine to methadone and buprenorphine, the two marketed drugs to treat opioid addiction and opioid withdrawal. What we found was a much cleaner profile. [Kratom] wasn't incredibly superior … but it seemed to be milder.*

It activates 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 a partial agonist …

Also, it activates a different signaling pathway once the receptor is turned on … It can be thought of as different inputs into a television … where the system is on but we're getting 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 the extent that other traditional opiate drugs do … Respiratory depression or stopping breathing is essentially 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-depressants. They will shut everything off."

How Kratom Eases Withdrawal Symptoms

As a therapeutic agent to help people get off opioids, kratom offers significant benefits. In the CNN news report above, Dr. Sanjay Gupta talks to two opioid addicts who kicked their habit with kratom, and interviews McCurdy about kratom's superior ability to serve as a **treatment for opioid addiction**.

It does, however, need to be regulated, McCurdy believes, to avoid the hazardous mixing with other far more dangerous drugs. It is this mixing, he claims, that is responsible for the deaths that have been linked to kratom.

So, just how does kratom work to curb opiate addiction? As explained by McCurdy, there are three traditional opioid receptors: mu, delta and kappa, all three of which are associated with numbing or dulling pain. In other words, they're analgesic receptors. They block or slow pain signal transmissions at the spinal cord level, so your brain doesn't process the pain signals as much.

Mu was named for its ability to interact with morphine. The mu receptor is responsible for the euphoric effects associated with opiates. It's also primarily responsible for respiratory depression. The delta receptor is also a target for selective analgesics, and does not appear to have as strongly addictive capabilities as the mu receptor.

Unfortunately, the delta receptor is linked to convulsions, and many drug trials aimed at the delta-selective opioid receptor had to be halted due to seizures that could not be resolved. Kratom does not appear to significantly interact with delta receptors.

The kappa opioid receptor, while good for killing pain, causes dysphoria — aversive-type feelings. "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," McCurdy says.

But when the human clinical trials began, the drug failed. "The people who took the drug said, 'I don't know what that was, but don't ever give it to me again.' They felt so awful they dropped out of the trials even after a single dose."

Abuse Potential of Kratom Appears To Be Low

Kratom appears to be a partial agonist for all of these receptors, only weakly affecting delta and kappa. But, if the mu receptor is the primary target, doesn't that mean kratom is addictive? At present, animal trials suggest the abuse potential of kratom is actually quite low. McCurdy explains:

> *"I have a paper under review right now in addiction biology with a colleague of mine, Scott Hemby, from High Point University in North Carolina … [looking] at what the actual abuse potential is for mitragynine. He trained rats to self-administer morphine.*
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> *They were able to learn to press a lever and they would get injections of morphine … Once you've 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 in 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 … 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 the animals to self-administer mitragynine to themselves over several doses. This 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."

Fresh Kratom Leaves May Be Safer Than Dried

Another compound in some processed and dried kratom products, 7-hydroxymitragynine, is known to be a full opioid agonist, and a very fast-acting and powerful one that does substitute directly for morphine and can be habit-forming. It does not appear to cause severe respiratory depression, however.

This compound is not present in fresh extracts, and McCurdy's team is trying to determine exactly how, when and why the compound is created. It could be an oxidative byproduct created during the drying process, or it could be the result of different growing regions, microclimates, the presence of certain insects or soil microbes, for example.

"I think what's even more interesting about this study we did — we treated animals with mitragynine that were already addicted to morphine, and then re-exposed them to morphine self-administration … It decreased their intake of morphine. This was pretty exciting, because it also shows that there's some 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 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."

Right now, the evidence is leaning toward 7-hydroxymitragynine being the result of oxidative stresses from drying the leaves, which suggests using fresh leaves to make tea, or taking an extract, would eliminate the risk associated with this oxidative metabolite, essentially eliminating the addictive potential of kratom. "That's our hypothesis right now," McCurdy says.

"We've been fortunate to gain collaborations with the University of Science, Malaysia, where they have actual cultivars of Mitragyna speciosa trees that they can use and study.

We've been studying fresh extract material from them under an agreement." McCurdy's team is also investigating traditional preparations made by users in Malaysia, and have received samples from trees grown in the native environment. None of the fresh samples have 7-hydroxymitragynine in detectable amounts.

Future Potential

McCurdy has created a modified kratom tea, in which certain alkaloids and plant chemicals were removed, thereby eliminating all side effects. Once perfected, this would be a patentable product that could be used therapeutically to counteract opioid

withdrawal symptoms without causing any. One obstacle that needs to be overcome is finding a verifiable kratom source that meets FDA standards to ensure public safety.

> *"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. You don't want to have the product being really good one day and not so good the other because the alkaloid content has changed from one batch to the other. You have to have batch-to-batch consistency,"* he says.

To solve this issue, he's working with horticulturists at the University of Florida to understand the conditions necessary to allow kratom to grow in the U.S., particularly Florida. Could they be grown in a greenhouse? What types of nutrients do they need? He's also been approached by commercial growers looking into the feasibility of growing 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,"* he says.

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

Current Legal Status of Kratom

Kratom is legal in most states, but not all. To check the legal status for your state, see **Speciosa.org's legality map**.[1] In Florida, kratom is legal in all areas except Sarasota, where kratom was banned. In the fall of 2016, the U.S. Drug Enforcement Agency (DEA) sought to add mitragynine, 7-hydroxymitragynine and kratom to the Schedule 1 of the Controlled Substances Act.

Schedule 1 means the substance has absolutely no medical use and is highly addictive. This classification essentially halts all research on the substance.

There was no science or evidence to back up the DEA's rationale, and the agency was contacted by a number of researchers expressing their objections. Researchers even contacted Congress for congressional intervention.

"Suffice it to say, there were many points of pressure on to the DEA to not make this scheduling official," McCurdy says. "The DEA decided to open up a 30-day comment period to obtain information. Scientists and people who have benefited from it flooded the DEA with messages."

The DEA received more than 23,000 individual comments urging them not to add kratom to Schedule 1. The opposition worked, and the DEA dropped it. This was largely a result of Chris Bell telling the story on Joe Rogan's podcast and encouraging their viewers to write in. Rogan's podcast has tremendous influence as this is the first time the DEA has overturned an action like this. I've included this historic podcast below for your convenience.

Still, the threat is there. They could, at any time, decide to make it illegal. "We had to actually shut down our research while that threat was underway, 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," McCurdy says.

About the Deaths Linked to Kratom

According to McCurdy, kratom has a "remarkable" safety profile. While there have been a few reported deaths associated with kratom in the U.S., most have been in combinations with other drugs.

A couple of cases have reported only finding kratom or mitragynine alkaloids in the deceased person's system, but in McCurdy's view, it's a tough sell that kratom alone would be responsible, as this herb has been used for hundreds of years in Malaysia and Thailand without any history of lethal consequences.

"We just don't know enough about how it's being metabolized," he says. *"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, 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. [They] drink it in the morning before they go to work. They drink it in the mid-afternoon …

Many of the men will gather in the evenings and drink a glass or two of kratom tea as they socialize … It's been safe for hundreds of years … Any death is a 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.

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 comes back to … getting a reliable source of the biomass … 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 linked to kratom."

Types of Kratom

There are four different types of kratom: red, white, green and Maeng Da. While the white and green are considered the same (the only difference is the timing of when the

leaves are picked), the red-veined version is different. Many claim the red-veined leaves have more alkaloids and the plant is a more potent version, but based on McCurdy's testing, the potency has less to do with the vein or strain and more to do with location.

> *"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 are the strongest — the red vein being — actually have the lowest [alkaloid] content compared to the products that are cheaper.*
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> *But, again, it's one of these things where there are no real labeling laws. There's no consistency. 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 … But from what we've seen in the natural environments, the difference is really going to be the microclimates …*
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> *The Maeng Da strain, touted as one of the high-end and superior strains, comes from a horn-shaped leaf called tooth leaves. 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."*

Teas and Extracts Can Be Made From Parts of the Kratom Tree

Traditionally, kratom has been used as a water extract and as tea made from the leaves. McCurdy has done a systematic study to evaluate various solvents, including ethanol, methanol and acetone, to determine the best extraction method. He's also studied the various extracts in animals, finding there are definitive differences between them. Extracts of bark, stems, roots and flowers have also been investigated.

> *"We do know there's a higher concentration of alkaloids in the vein than there is in the flesh of the leaf material,"* he says. *"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 … One other thing I find really fascinating is the bark or the branches. If people feel they need a boost, they will put the bark branches into their tea 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 … We haven't seen much of a difference outside of the leaves. There are different compounds, of course … that are in higher quantities in the stems [and] fruits. We're trying to pursue and see what the pharmacology is that's associated to them …

Most of the time that people brew 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. But the water extract will concentrate it better."

Even Kratom Should Be Used With Caution

While kratom appears to have a favorable safety profile compared to opioids, this isn't to say that kratom usage is without risk and can be used without concern. It's important to recognize that kratom is a psychoactive substance and should not be used carelessly. There's still very little research showing how to use it safely and effectively, and it may have a very different effect from one person to the next.

Also, while it may be useful for weaning off opioids, certain types of kratom could potentially be addictive. So please, do your research before trying it. One place to start is the American Kratom Association.[2] Also know there are many other safe and effective alternatives to prescription and over-the-counter painkillers. If you're looking for safer options for pain relief than opioid drugs, please see these options for treating pain without drugs.

Sources and References

- [1] Speciosa.com Kratom Legality Map
- [2] American Kratom Association