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Short Communication

# Observations on Mitragynine Use

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## ABSTRACT

Mitragynine is the principal alkaloid found in the leaves of kratom *(Mitragyna speciosa)*, a tropical tree indigenous to Southeast Asia Thailand, Malaysia, and Papua New Guinea. Mitragynine has become a drug of interest because of its increased use among substance abusers and patients seeking pain relief. Often the use of this drug is not disclosed by patients testing for the drug is possible because of recent advances in laboratories using LC-MS/MS and/or LC-TOF and the availability of appropriate standards. We observed the median amount of drug in urine to be 88 ng/mL we documented about a three=fold increase in the use of this drug over the past five years in our population of pain and substance abuse patients undergoing urine drug monitoring.

**Keywords:** Mitragynine; Kratom leaves; Overdose; Opioids

## ABOUT THE STUDY

Mitragynine is the principal alkaloid found in the leaves of kratom *(Mitragyna speciosa)*, a tropical tree indigenous to Southeast Asia Thailand, Malaysia, and Papua New Guinea used by indigenous population historically as a stimulant to enhance stamina and reduce fatigue [1]. The plant has been used for its psychoactive and analgesic properties throughout Southeast Asia since the 1800s. In South East Asia, kratom is used as an antidiarrheal, a cough suppressant, an antidiabetic, an intestinal deworming agent and as a wound poultice. Most recently it is also used as an aid in treatment of heroin addiction.

Outside Asia, anecdotal use of kratom preparations for self-treatment of chronic pain and opioid withdrawal symptoms and as a replacement for opioid analgesics have been reported [2]. The raw leaves of the plant can be chewed, or dried and macerated to be smoked, steeped in tea or encapsulated. These products are available through the internet as herbal plant material or extract [3].

Fresh or dried kratom leaves are chewed or drank as a tea. Sugar or honey is added to mask the bitter taste. Lemon juice is often added to facilitate the extraction of the active ingredient. Less commonly the leaves can be dried and smoked. Prepared as cold cocktail containing leaves, a caffeinated soft drink with codeine-containing cough syrup. Users in Southeast Asian countries remove the stems from the leaves before eating. Salt is added to prevent constipation. The chewed material is swallowed, chased with warm water, coffee or sugar syrup. Kratom users chew one to three fresh leaves at a time.

Mitragynine has become a drug of interest because of its increased use among substance abusers and patients seeking pain relief. Often the use of this drug is not disclosed by patients with toxicological symptoms making the cause of their symptoms difficult. Testing for the drug is possible because of recent advances in laboratories using LC-MS/MS and LC-TOF and the availability of appropriate standards.

The active ingredient, mitragynine, is lipophilic and moderately permeable. Consumed orally, absorption is roughly 20%whereas complete bioavailability can be seen through intravenous administration [2]. When consumed at low doses stimulant effects are observed including increased energy, alertness, and euphoria. Larger doses produce opiate analgesia and sedation [4]. Mitragynine acts as an agonist via mu-opioid receptors. Administration of naloxone has been shown to block its opiate like effects [5]. The plant is used as a substitute for other opiates and to relieve the symptoms of opiate withdrawal. However, it can produce its own withdrawal symptoms including nausea, itching, aching, anorexia, insomnia, and psychological disturbance.

Currently various forms of kratom such as leaves, (dried or

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crushed), extracts, powders, capsules, tablets, liquids, and gum/resin are available on the internet. These products often advertise the stimulatory effect of kratom and that it has the benefit of counteracting opioid withdrawal. The study was approved by ASPIRE IRB Santee CA. The analysis of 2,334,000 urines by the LC-MS/MS method of Krock, et al. [6], included a quantitative detection of mitragynine.

Kratom is not currently scheduled under the controlled substances act. However the DEA has issued an advisory calling attention to dangers of its use listing it as a Drug and Chemical of Concern. [4]. Kratom has not been approved by the FDA for any medical use. Legality has been left to state legislation with some states imposing regulation or prohibition against possession and use

Several active components of kratom have been identified. Mitragynine is the most abundant alkaloid in the leaves with activity on μ, δ, and κ receptors. One of its main effects is on μ receptors creating opiate and analgesic effects and physical dependence. A second component of the leaves is 7-hydroxymitragynine which comprises about 2% of the alkaloids in the leaves and has a 13 to 46-fold higher potency than morphine and mitragynine, respectively.

There is concern that kratom overdoses can cause death. The CDC conducted a retroactive study of fatal overdoses from 27 states. That data included 27,338 deaths where 152 were kratom positive. Of those 152, 91 were determined to be caused by kratom. These estimates were probably low because postmortem toxicology protocols for each state, county or city may not test for kratom [7-9].

Precision diagnostics is a reference laboratory that commonly tests for mitragynine in urine using LCMS instruments with the low cutoff of 5 ng/mL. For this study, the results 2,112,987 specimens tested for mitragynine are shown. The increase in the use of mitragynine between April 2016 and October 2020 as a percentage of total specimens tested is illustrated in Figure 1. From 2016 to 2020 the percent of drug screens positive for mitragynine increased from about 0.2% to 0.6%, an overall increase of 3-fold. The frequency distribution curve presented in Figure 2 shows most of the observations were in the 10 to 100 ng/mL range. However, because of the sharp drop-off at 5 ng/mL, more patients were not included because they were below the cutoff.

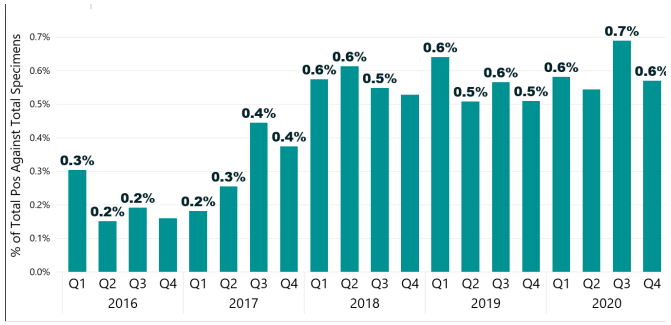


**Figure 1:** Percent of drug test specimen's positive for mitragynine.

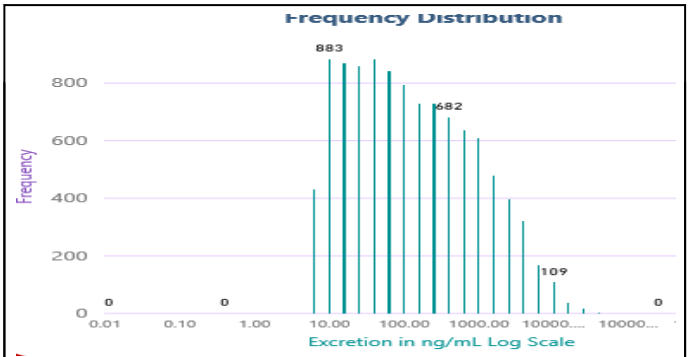


**Figure 2:** Frequency distribution versus concentration for all positive mitragynine specimens.

The urines are also tested for several opioids, benzodiazepines, and illicit drugs such as fentanyl and cocaine (benzoylecgonine) [6]. This offered an opportunity to gain some insight into the mitragynine drug user habits. Of the 10,274 specimen's positive for mitragynine, we observed that about 33% of mitragynine positive specimens were positive for the opioid's morphine, oxycodone and hydrocodone, and about 23% were also positive for benzodiazepine use (Table 1). About 6% of the subjects used cocaine, while a similar 5% were positive for fentanyl.

| | | |
|---|---|---|
| Mitragynine positive | 10,274 | |
| +Morphine | 873 | |
| +Hydrocodone | 1235 | |
| +Oxycodone positive | 1321 | Total opiates 3429 |
| Amino clonazepam | 879 | |
| Alpha hydoxy alprazolam | 778 | |
| Oxazepam | 744 | Total benzos 2401 |
| Fentanyl | 557 | |
| Cocaine | 626 | |

**Table 1:** Mitragynine and other drug use.

## CONCLUSION

This also illustrates FDA warnings about the drug. The Food and Drug Administration (FDA) commissioner has stated that we must remain vigilant and aggressive against trends that threaten to reverse our progress as we deal with the devastating crisis of opioid misuse and overdose plaguing our nation. He addressed the dangers associated with rise in the use of kratom, addressing marketers making claims for therapeutic effects for products containing the plant commonly known as kratom, a botanical with potential for abuse. These observations are consistent with other studies that show that the drug is valued for its opioid like properties.

## CONFLICT OF INTEREST

There are no conflicts of interest.

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