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Kratom: The Herbal Opioid

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Abstract

Objective: Kratom (*Mitragyna speciose*) is a tropical tree used in traditional herbal medicine. It has gained popularity as an herbal remedy and recreational drug. Bioactive alkaloids isolated from kratom shows stimulant and opiate-like effects and raise concern for potential abuse, dependence, and toxicity. The intent is to characterize the association of kratom use with toxicity-related deaths, determine the profile of mixed-drug usage, characterize the demographics of those using kratom, and to identify opportunities for public health interventions.

Methods: This is a retrospective study of postmortem toxicology from suspected drug-related deaths from January 2018 to March 2019. The data was aggregated from the Wayne County and Washtenaw County Medical Examiners' Offices, which serve Livingston, Monroe, Wayne, and Washtenaw counties in the State of Michigan. Thirty-three (33) decedents with postmortem toxicology positive for the kratom compound mitragynine were identified in suspected drug-related deaths; none were excluded.

Results: We examined the demographics and co-occurring drug profiles in mitragynine-related drug deaths. Of 33 identified cases, 31 (94%) were certified as drug toxicity-related deaths. Decedents were predominantly male (88%) and Caucasian (94%) with a median age of 36 years and with known substance abuse history (80%).We examined the demographics and co-occurring drug profiles in mitragynine-related drug deaths. Of 33 identified cases, 31 (94%) were certified as drug toxicity-related deaths. Decedents were predominantly male (88%) and Caucasian (94%) with a median age of 36 years and with known substance abuse history (80%). Co-occurrence of opioids was observed in 84% of cases with fentanyl being most common. Stimulants such as cocaine and amphetamines were found in 52%. In cases where mitragynine was determined to be contributory to death, the median concentration was 180 ng/mL. A single-agent mitragynine death was confirmed in one decedent (2400 ng/mL).

Conclusion: In the medical examiner setting, kratom found in postmortem toxicology is rising and associated deaths are no longer esoteric. Kratom positivity has a strong association with substance abuse history and mixed-drug toxicity suggestive of recreational use. Despite backlash from consumers and advocacy groups, the known potential for abuse and increasing evidence of toxicity likely warrants some measure of regulation.

Keywords: Kratom; Mitragynine; Drug Abuse; Drug Dependence; Toxicology; Postmortem Toxicology; Herbal Medicine; Opioid; 7-hydroxymitragynine

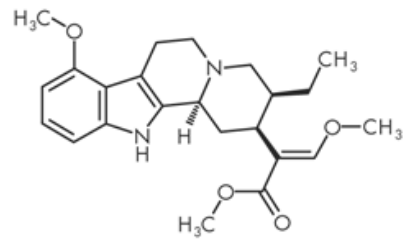
Introduction

Mitragyna speciosa, commonly known as kratom, is a tropical tree native to Southeast Asia. It has a long history of traditional uses for ailments such as fever, diarrhea, diabetes, stress, fatigue, and pain [1,2]. In recent years, kratom has entered the Western herbal and recreational drug market and is touted by many as a safe and legal psychoactive substance that improves mood, relieves pain, and may possess medicinal qualities to combat opioid addiction [3,4]. In the United States, kratom can be purchased as leaves, powders, gums, resins, capsules, pills, and extracts for consumption, traditional smoking, and smoking in electronic cigarettes. Some formulations advertise up to 80-fold concentration of active compounds over dry leaves. The increasing popularity of kratom has resulted in serious public health concerns [4-6].

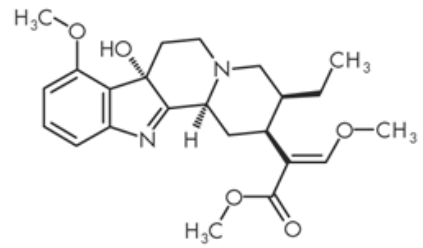
During a six-year period, from 2011 to 2017, kratom exposure was reported in more than 1800 cases to poison control centers with more than half of exposures being reported in 2016-2017 [4]. The report indicated that exposures were most commonly intentional. Serious medical outcomes were documented in approximately 50% of cases and included seizures, respiratory depression, coma, bradycardia, rhabdomyolysis and renal failure, and respiratory and cardiac arrest. In an overlapping 17-month period from July 2016 to December 2017, there were 152 unintentional overdose fatalities positive for kratom reported to the State Unintentional Drug Overdose Reporting System [5] (SUDORS, collected from 10 states, and partial data from 17 additional states). In approximately 60% of those reports kratom was determined to be the cause of death, and in the remainder it was found in mixed-drug toxicities where the contribution of kratom was undetermined.

The active alkaloids in kratom have dose-dependent effects causing low-dose stimulant and high-dose opioid-like effects [7,8]. Two compounds isolated from kratom, mitragynine and 7-hydroxymitragynine, are thought to mediate the majority of its effects

(Figure 1). It has been reported that mitragynine and 7-hydroxymitragynine function as partial agonists at the human μ-opioid receptor, and both exhibit analgesic effects [9,10]. Mitragynine has a potency three to five times that of morphine and 7-hydroxymitragyine is approximately 40-fold more than mitragynine. Both compounds were found to be G-protein biased agonists without recruitment of the beta-arrestin pathway, which is thought to limit respiratory depression and mitigate the inhibitory effects on gastrointestinal motility [9-11]. These compounds mediate the physiologic effects that leave users feeling elevation in mood and energy, reduced anxiety, increased sociability, analgesia, and euphoria [12]. The abuse and addiction potential is well-documented [2,8,13].



Mitragynine [$C_{23}H_{30}N_2O_4$ (398.50 g/mol)]



7-hydroxymitragynine [$C_{23}H_{30}N_2O_5$ (414.50 g/mol)]

Figure 1: Active compounds in Kratom. Mitragynine is the most abundant alkaloid in Kratom. 7-Hydroxymitragynine is present in very small amounts in kratom leaves, however, shows approximately 40-fold greater potency. Early studies of the pharmacokinetics reveal a maximum plasma concentration at 0.83 hours with oral administeration, with a terminal half-life of approximately 24 hours. Estimates in the volume of distribution range from 14-62 L/kg. Both compounds are believed to be G-protein biased μ-opioid receptor agonists. Further studies are necessary to identify any additional compounds in kratom that may play a role in drug-drug interactions.

An initial study of the pharmacokinetics of kratom compounds was done in ten healthy Thai male chronic users. The study was completed without adverse reactions. The time to reach maximum plasma concentration following oral administration of kratom tea was 0.83 ± 0.35 hours with terminal half-life of 23.24 ± 16.07 hours. The apparent volume of distribution was estimated at 38.04 ± 24.32 L/kg. Less than 1% was excreted non-metabolized in the urine [14].

Southeast Michigan, home to Detroit, Michigan, is significantly affected by the opioid epidemic with approximately 900 opioid-related fatalities reported in 2018 alone. This makes the region especially vulnerable to kratom and kratom-like drugs due to their availability, reduced cost, legality, and promise to help treat addiction.

We studied the appearance of kratom in overdose deaths between January 2018 and March 2019 *via* postmortem samples from the Wayne County and Washtenaw County Medical Examiners' Offices. We tried to determine if there was an increasing prevalence of kratom use, if use was associated with toxicity-related deaths, to characterize the drug profile of mixed-substance usage in kratom users, and to determine the demographics of those using kratom to identify opportunities for public health intervention.

Materials and Methods

Postmortem toxicology was collected on all autopsied cases suspicious for drug-related death. Peripheral blood from the iliac vein was used [15]. All toxicology testing was submitted to National Medical Services (NMS labs, Horsham, PA) and analyzed using an extended screening panel for postmortem toxicology, which investigates a predefined selection of drugs of abuse (including mitragynine) and therapeutic drugs or their associated metabolites. Presumptive positive findings for mitragynine as determined by liquid chromatography time of flight mass spectrometry were confirmed and quantitated by liquid chromatography/tandem mass spectrometry (LC-MS/MS) with a reporting limit of 5.0 ng/mL for mitragynine.

Using CaseManager$_{fw}^{TM}$ (Wayne County Office; QuincyTech, Woodbridge, CT) and MDILog® (Washtenaw County Office; Big Rapids, MI) software systems, 33 cases positive for mitragynine were identified during the period of January 2018 to March 2019. Prior to 2018, mitragynine was not quantified. No cases were excluded from the study. Thorough evaluation of death scene investigations, next-of-kin interviews, and medical records were used to determine documented history of substance abuse. The Michigan Automated Prescription System (MAPS) was used to determine the history of prescribed controlled-substances in the period of 24-months prior to death. A two-to-one age and sex-matched control group (mitragynine negative, toxicity related deaths) was identified for comparison of mixed-drug profiles.

Results and Discussion

In contrast to a recent study [6] that identified 15 cases over an eight year period (1999-2017), we identified 33 cases in a 15-month period (January 2018 to March 2019) suggesting a significant increase in use of kratom and a unique substance use profile for a subsect of southeast Michigan (Table 1). The group was overwhelmingly male (88%) and Caucasian (94%) with a median age of 36 years. Of 33 cases positive for the kratom compound mitragynine, 31 (94%) were certified as drug toxicity-related deaths (TRDs) and mitragynine was identified in the death certificate as either an immediate (Part I) or contributory (Part II) cause of death. A total of eight cases (8/33) determined that mitragynine did not contribute in the cause of death; six of these cases identified other drugs, namely fentanyl, and two were determined to be of natural causes. *Via* investigation, evidence of known substance abuse history was confirmed in 80% of cases. Investigation of the Michigan Automated Prescription System (MAPS) revealed 61% of decedents had a prescribed controlled pharmaceutical in the 24-months prior to death (Table 2). The calculated Overdose Risk score, provided by MAPS, indicated that the study individuals with MAPS histories had a 20-fold increase in overdose risk compared to the general population. This risk score was based on multiple factors, including: a mean of 29 prescriptions for controlled substances per decedent, mean of 6 medical providers per decedent, and mean of 4 pharmacies per decedent in the 24-month period prior to death. Interestingly, 16 of 19

(84%) known prescription drug users had no active prescriptions for controlled substances at the time of death and only one decedent was positive for a prescribed controlled substance on postmortem toxicology.

Examination of the 25 cases which had mitragynine listed on the death certification showed an average mitragynine concentration of 324.9 ng/mL (median value of 180 ng/mL, Tables 3a and 3b).

Kratom (mitragynine) positive cases	**33**
Sex	
Men	29 (88%)
Women	4
Age (Median)	36 years (range 21-58 years)
Race	
White	31 (94%)
Black	0
Asian	1
Other	1
Cause of death	
Toxicity-related (TRDs)	31 (94%)
Mitragynine (COD^+)	25 (81%)
Manner of death	
Accident	29
Suicide	1
Natural	2
Indeterminate	1
History of substance abuse	25/31 (80%)

Table 1: Demographics of Kratom-Positive Deaths. We identified 33 decedents who were investigated for a drug-related death and were positive for mitragynine, the active compound in kratom. The studied group was largely composed of white males in their mid-30. Women appear to be underrepresented, as were blacks. Thirty-one cases were identified as toxicity-related deaths (TRDs). Mitragynine was listed in either the immediate cause of death (Part I of the death certificate) or as a contributing factor (Part II) in 81% of TRDs (COD^+). A total of eight cases did not list mitragynine as contributory; six TRDs had mitragynine on the postmortem toxicology, and two deaths were due to natural disease (complication of obesity and cerebral aneurysm). A history of substance abuse/dependency was confirmed in 80% of TRDs.

MAPS Data (24-months from time of death)	
History of prescribed controlled substances	19/31 (61%)
Overdose Risk Score	Mean 390 (high 690)
Number of Rx	29.2 (67)
Number of providers	6.1 (31)
Number of pharmacies	4.0 (16)
Active prescriptions for controlled substances	3

Table 2: The Michigan Automated Prescription System (MAPS) revealed 61% of TRDs had a prescribed controlled substance in the 24-months prior to death, with three decedents with active prescriptions at the time of death. The mean overdose score is calculated by MAPS using known risk factors such as number of prescriptions, providers, pharmacies, including others. A score of 250 is roughly equivalent to a 10-fold increase in overdose risk over the general population. The calculated risk indicated a mean 20-fold increase over the general population, with a high of 132-fold increase (score of 690).

Mitragynine (COD^+)	324.9 ng/mL (mean)
	508.8 ng/mL (SD)
	180 ng/mL (median)
	2390.5 ng/mL (range)
Mitragynine (COD^-)	64.5 ng/mL (mean)
	65.5 ng/mL (SD)
	33.0 ng/mL (median)
	156.0 ng/mL (range)

Table 3a: Concentration of Mitragynine in Toxicity-Related Deaths. Kratom positivity was determined by the presence of mitragynine, the primary active alkaloid in postmortem blood collect from the iliac vein. In cases where mitragynine was determined to be contributory to the cause of death, there is a 5-fold increase in mean concentration (324.9 vs 64.5 ng/mL).

Compounds	**$COD^{(+)}$**	**$COD^{(-)}$**
Opioids	84%	67%
Stimulants	52%	67%
THC	45%	33%
Benzodiazepines	39%	50%
Antidepressant	32%	33%
Alcohol	19%	17%

Table 3b: Drug co-occurrence with Mitragynine Positivity. Co-occurrence with opioids was found in 84% of cases with fentanyl specifically identified in 71% of cases with a mean concentration of approximately 30 ng/mL, stimulants such as cocaine and amphetamines were found in roughly half of cases.

There were six TRDs which did not have mitragynine listed on the death certificate; those showed a mean mitragynine concentration of 64.5 ng/mL. Similar to recent reports [5], fentanyl was identified as the most common co-occurring drug (71% of cases). The presence of fentanyl and other opioids, including the presence of carfentanil (one case), were observed in 84% of cases where mitragynine was

contributory to death. Stimulants, such as cocaine and amphetamines, were found in 52% of cases. Most cases (96%) were found to be mixed-drug related fatalities [16].

Analysis of drug co-occurrence confirmed that opioid use is by far the most prevalent (Table 3c). In this group, co-occurrence of opioids with benzodiazepines, stimulants, alcohol, THC, and antidepressants was 78-100%. Specifically, 88% of cases with stimulants present (such as cocaine and amphetamines) had co-occurrence of opioids, namely fentanyl of 25 cases where mitragynine was contributory to death, 15 (60%) had a mixed-drug toxicity of two or more drug classes (opioids, benzodiazepines, stimulants, alcohol, THC, and antidepressants). Interestingly, the use of stimulants was highly correlated with benzodiazepine and alcohol use, 88% and 63% co-occurrence, respectively. On the other hand, benzodiazepine and alcohol use was negatively correlated with THC use, 11% and 8% co-occurrence, respectively.

		Opioids	BZ	Stimulants	Alcohol	THC	Antidepressant
Observed Drug	Opioids	-	32%	32%	46%	23%	46%
	BZ	78%	-	33%	56%	11%	33%
	Stimulants	88%	88%	-	63%	38%	50%
	Alcohol	83%	42%	42%	-	8%	50%
	THC	100%	20%	60%	20%	-	40%
	Antidepressant	83%	25%	25%	50%	17%	-

Table 3c: Co-Occurrence of Drugs in Mitragynine-Positive, (COD^+) cases. Decedents who were positive for opioids were also found to be positive for stimulants 32% of the time. Individuals who were positive for stimulants were concurrently using opioids (88%) and benzodiazepines (88%). Findings indicate a high degree of mixed-drug toxicity and intentional recreational use. Opioids refers to all morphine-like and fentanyl-like compounds; BZ, benzodiazepines; stimulants refers to cocaine and metabolites, amphetamine, and MDMA.

Kratom negative control cases	66
Sex	
Men	56 (85%)
Women	10
Age (Median)	34
Race	
White	48 (73%)
Black	13
Other	5
Cause of death	
Toxicity-related (TRDs)	66
Manner of death	
Accident	66

Table 4a: Drug profiles of kratom-negative cases. A 2-to-1 randomized, age and sex matched, control group of toxicity related deaths was identified for comparison of mix drug toxicity (66 decedents).

An age and sex matched control group of 66 decedents was identified (Table 4a and 4b) from the same time period. Investigation of drug co-occurrence among the control group vs. the mitragynine (COD^+) group identified many similarities in the concurrent use of opioids (89% vs. 84%), stimulants (56% vs. 52%), and benzodiazepines (41% vs. 39%). Significant differences were identified in the percent co-occurrence of alcohol (29% vs. 19%), antidepressants (18% vs. 32%) and barbiturates (8% in the control vs. not identified in the mitragynine (COD^+) group). Examination of mixed-drug toxicity cases revealed 15 (48%) of mitragynine (COD^+) cases had three or more of the identified drug classes present; similarly, 35 (53%) of the control group was using three or more of the reported drug classes, concurrently.

Drug	Percent co-occurrence
Opioids	89%
Stimulants	56%
Benzodiazepines	41%
Alcohol	29%
THC	29%
Antidepressant	18%
Barbiturate	8%

Table 4b: Percent Co-Occurrence of Drugs in Mitragynine negative cases co-occurrence of opioids and stimulants appear roughly the same in comparison to mitragynine (COD^+) cases. Significant differences were identified in the percent co-occurrence of alcohol (29% vs. 19%), antidepressants (18% vs. 32%) and barbiturates use (not detected in mitragynine positive cases).

In one case, a 21-year-old white male with a history of heroin abuse and remote kratom use was found unresponsive in a suspected drug-related death. Autopsy identified no significant abnormalities. Postmortem toxicology performed on the decedent's peripheral blood revealed 2,400 ng/mL of mitragynine (Table 5). Investigation found that he had again started using kratom in the form of pills two weeks prior to death due to symptomatic pain. Although cases of single-agent death like this are less common, they do exist and are being

increasingly reported [6]. Based on personal communications (NMS, Horsham, PA), it appears that single agent deaths are associated with significant blood concentrations (>1,000 ng/mL).

Postmortem toxicology report of fatality due to Kratom (mitragynine) toxicity	
Caffeine	Positive
Cotinine	Positive
Naloxone	Positive
Clonazepam	3.8 ng/mL
7-Amino Clonazepam	130 ng/mL
Lamotrigine	5.6 mcg/mL
11-Hydroxy Delta-9 THC	17 ng/mL
Delta-9 Carboxy THC	250 ng/mL
Delta-9 THC	46 ng/mL
Hydroxyzine	1000 ng/mL
Amphetamine	8.8 ng/mL
Mitragynine	2400 ng/mL

Table 5: Postmortem toxicology of single agent fatality due to kratom use in a 21-year-old white male found unresponsive at his residence. Lamotrigine and clonazepam were confirmed prescribed drugs and within normally published therapeutic ranges. In consideration of the circumstances, postmortem examination, and postmortem toxicology the mechanism of death was certified as mitragynine toxicity and the manner of death as accident.

Conclusion

Kratom use is on the rise. Where kratom-related death was a rare case study, it is now well-known among the forensic community. Deaths appear to be strongly associated with substance abuse history and mixed-drug usage. The prevalence of mixed-drug usage suggests intentional and recreational behavior; however, the effect of mitragynine on other co-occurring compounds requires further study.

The degree and character of mix-drug toxicities appear to be similar when compared to drug related deaths in the absence of mitragynine, indicating that, in the medical examiner setting, the drug use tendencies of decedents using kratom is roughly the same as non-kratom users. Kratom users were found to have nearly two-fold increase in antidepressant usage, possibly a reflection of the socio-economic differences between kratom and non-kratom users reflected in the access to healthcare.

There is a growing concern and call for regulation of kratom and equal backlash from consumers and advocacy groups heralding it as a remedy specifically for use in the treatment of opioid dependence and addiction. In August 2016, the Drug Enforcement Administration (DEA) announced its intent to place the active compounds found in kratom into the Schedule I of the Controlled Substances Act "in order to avoid an imminent hazard to public safety". By October 2016, due to the resultant widespread public backlash (demonstrations, petitions) and calls by Congress, the DEA reconsidered emergency scheduling in favor of solicitation of public comments. Currently, debate continues, and scheduling appears to be forthcoming to the chagrin of advocacy groups. Whether or not kratom holds the potential to be developed for medical use or treatment for opioid dependence remains to be seen; however, it should not mitigate the dangers inherent in substance abuse.

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