Kratom-Associated Fatalities in Northern Nevada—What Mitragynine Level Is Fatal?

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Abstract: *Mitragyna speciosa*, commonly known as the kratom tree, has been utilized in Southeast Asia for centuries for its opioid-like effects. Kratom has been available in the United States for the past decade and has grown increasingly popular despite a lack of clinical research to determine its safety. With its widespread use, there have been an increasing number of fatalities. This study aims to establish a potential lethal range for mitragynine, the active compound in kratom, by investigating the toxicology reports of 35 deaths in Northern Nevada between 2015 and 2020. Mitragynine concentrations ranged from 8.7 to 1800 ng/mL (n = 27) in cases with drug toxicity as the cause of death; in 1 case, the sole intoxicant was mitragynine with a blood concentration of 950 ng/mL. In cases with nonmitragynine causes of death, the concentration was 110 to 980 ng/mL (n = 8). There was no statistically significant difference in blood concentrations between cases where mitragynine was not listed as a cause of death (mean, 315 ± 297.2 ng/mL) and cases in which mitragynine contributed to death (mean, 269.4 ± 382.5 ng/mL; $P < 0.201$). A literature review is also presented.

Key Words: fatalities, kratom, lethal, mitragynine, toxicity

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Thousands of miles away from Reno, Nevada, in Southeast Asia, grows a tropical tree, *Mitragyna speciosa*, commonly referred to as the kratom tree. The leaves of the kratom tree have been utilized for centuries, both medicinally and recreationally, for their opioid-like effects at higher doses and stimulant-like effects at lower doses.[1] The active compounds within kratom are mitragynine and 7-hydroxymitragynine (7-HMG), indole alkaloids, which act as μ-, κ-, and δ-opioid partial receptor agonists.[2] This agonistic capability gives kratom users similar adverse effects that are experienced with other opioid use. Despite the lack of clinical research, proponents of kratom use claim the drug is not associated with the detrimental adverse effects that traditional opioids have, such as dependence and toxicity. The lack of knowledge regarding kratom's safety and efficacy has partially contributed to the use of this extract becoming widespread, in addition to its being largely unregulated.

Kratom contains a variety of alkaloids including mitragynine, 7-HMG, mitragynine pseudoindoxyl, speciogynine, speciociliatine, and paynantheine.[3] The active alkaloid content of kratom consists of mitragynine (66%) and 7-HMG constituting 2%.[4] The most abundant alkaloid, mitragynine, is metabolized by the enzyme cytochrome P450 3A4 to the more potent μ-opioid agonist, 7-HMG. Furthermore, in a mechanism not quite understood, the 7-HMG is then metabolized in the blood to an even more potent μ-agonist, mitragynine pseudoindoxyl.[3] While it is evident mitragynine undergoes metabolism to many active metabolites, there is a lack of research regarding the specific percentages of kratom and its active metabolic derivatives.

Kratom has grown in popularity in this nation because of the ease of access. Kratom is legal in all but 6 states and can be easily obtained from the internet and in local convenience stores across the country.[5] According to the Drug Enforcement Administration, as of April 2020, kratom is not regulated under the Controlled Substances Act and has not been approved by the US Food and Drug Administration for medical use.[6] The number of phone calls placed to the US Poison Control Center for kratom exposure increased 10-fold between 2010 and 2015.[7] As of 2021, it has been estimated that 0.8% (2,031,803) of adults in the United States have used kratom within the last year.[8] In the past decade, particularly in the past 5 years, its usage has only continued to increase, leaving behind a string of associated fatalities. This study examines postmortem blood levels of mitragynine in 35 deaths in Northern Nevada from 2015 to 2020 in which mitragynine was detected on toxicological analysis. A review of the literature is also presented.

MATERIALS AND METHODS

A retrospective review of cases with quantitated mitragynine blood levels, with statistical analysis and comparison to prior published drug levels, was conducted. Research was done at the Washoe County Regional Medical Examiner's Office in Reno, Nevada, from March to May 2020. Washoe County Regional Medical Examiner's Office's VertiQ case management database was queried for "mitragynine" to generate a list of cases from 2015 to 2020 (2015 being when mitragynine was first detected in postmortem samples in the office). Only cases that had a quantitative value for mitragynine detected in the blood by high-performance liquid chromatography/tandem mass spectrometry were selected; liquid chromatography/tandem mass spectrometry was performed by the National Medical Services Laboratories. Based on death certificate review, the cases were assigned to 2 groups: group 1 consisted of death certificates in which mitragynine was listed as part of the cause of death or as a contributory condition; in group 2, mitragynine was detected on toxicology testing but not listed as a cause of death or contributory factor. Data extracted from the 35 case files included age, cause of death, body mass index (BMI), gender, toxicology results, and notes from assessments made during autopsy. Data are expressed as mean ± SD. Mann-Whitney *U* test, a nonparametric test, was used to evaluate for statistical significance between the 2 groups' values. $P < 0.05$ was considered significant. The Pearson correlation coefficient (r) was calculated to assess the strength of a linear relationship between BMI and mitragynine levels in peripheral postmortem blood.

RESULTS

A total of 40 cases were identified in which mitragynine had been detected; however, 5 cases were not included in further analysis because the result was qualitative only, and no quantitative value was reported. The remaining 35 cases included 27 cases that

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had mitragynine listed as part of the cause of death or as a contributory condition and 8 cases that had mitragynine detected on toxicology testing but not listed as a cause of death or contributory factor. Thirty of the cases were autopsied; 3 had an external examination with medical records review, and 1 case had a records review with toxicology testing on antemortem hospital blood due to length of hospitalization. In all cases in which an autopsy, external examination, or records review was performed, cause of death determination was made by board-certified forensic pathologist (American Board of Pathology). The single case that did not receive any examination or review was a sheriff-coroner case that was not referred to the Washoe County Regional Medical Examiner's Office; a toxicology specimen was drawn at the scene by a sheriff-coroner. The cause of death was trauma (gunshot wound) that was obvious at the scene, and mitragynine's presence was an incidental finding. All blood samples were postmortem peripheral blood except for 4 cases: 2 postmortem central blood samples and 2 antemortem hospital admission blood samples.

In the 27 cases with drug toxicity as the cause of death, mitragynine concentrations ranged from 8.7 to 1800 ng/mL; in the case with mitragynine as the sole intoxicant, the blood concentration was 950 ng/mL. Other notable substances detected on toxicology included opioids in 81.5% (n = 22) of the cases, benzodiazepines in 33.3% (n = 9), ethanol in 33.3% (n = 9), amphetamine/methamphetamine in 25.9% (n = 7), and nitrous oxide in 7.4% (n = 2). The only other substance detected in the case where mitragynine was determined to be the sole substance causing death was aripiprazole, an atypical antipsychotic, at 310 ng/mL. However, it is to be noted that phenibut was found at the scene. Toxicology testing was not available for the substance at the time, and thus, it cannot be ruled out as a possible contributor to the death. The demographics and toxicology results for these cases are described in Table 1.

In 8 cases with other causes of death, mitragynine concentrations ranged from 110 to 980 ng/mL; demographics and toxicology results for these cases are described in Table 2. There was no statistically significant difference in postmortem blood concentrations of mitragynine between cases in which mitragynine was detected in blood but not listed as a cause of death (mean, 315 ± 297.2 ng/mL) and cases in which mitragynine caused or contributed to death (mean, 269.4 ± 382.5 ng/mL, $P < 0.201$). There was a moderate positive association between BMI and postmortem blood mitragynine concentrations in cases in which mitragynine was listed on the death certificate as part of the cause of death or contributory condition ($r = 0.46$; Fig. 1). One case was omitted from Figure 1 as there was no BMI, height, or weight provided because it was a delayed drug overdose death during hospitalization; hospital blood from the time of admission was the toxicology specimen tested, and no body examination was completed.

LITERATURE REVIEW

A total of 127 fatalities due to kratom toxicity were found in the medical literature, within 11 publications.[9–19] Of these 127 cases, 10 were fatalities in which kratom was the sole intoxicant, whereas the other 117 cases were due to combined drug toxicity. For the cases with fatalities due to combined drug toxicity, the blood levels of mitragynine ranged from 10 to 4800 ng/mL as seen in Table 3.[9,10,12–14,16–18] Of the 10 fatalities due to mitragynine, only 3 had quantified values reported: 260, 1400,[11] and 1900 ng/mL, respectively, in blood.[15] Numerical data were the only information provided for the majority of these cases, but the case with the greatest value recorded, 1900 ng/mL, was also the most descriptive. This case reports the case of a 33-year-old man of athletic build and 21-year history of varied substance abuse. The death investigation revealed no evidence of an intentional death, but rather an accidental overdose via kratom.[15]

The study by Olsen et al[19] was omitted from the table because of the quantity and manner of data it compiled, as it was a Centers for Disease Control and Prevention–funded project evaluating opioid overdose deaths from 2016 to 2017 in 27 states. From the 27,338 cases evaluated, kratom was present in 152 cases. Kratom contributed to COD per a medical examiner or coroner in 91 cases, and other substances listed on the toxicology report that contributed to COD included the following: 56% (n = 51) with fentanyl or analogs, 49.5% (n = 22) with opioids, 26.4% (n = 24) with benzodiazepines, 16.5% (n = 15) with cocaine, 25.3% (n = 23) with heroin, and 12.1% (n = 11) had alcohol detected.[19]

DISCUSSION

Sipping on tea, smoking the leaves, and swallowing kratom capsules are a few ways these herbal extracts get into the human body. Without much guidance and no standardization of product potency, it can be difficult for users to determine the exact concentration of kratom they are consuming, and does anyone know how much kratom is too much?

While kratom was detected in all 35 cases included in this study, only 27 had causes of death found to be related to the substance. The cases from Table 2, along with their presentations that lead to the determination of other causes of death, are as follows: cases 1, 3, and 7 were all obvious traumatic deaths due to gunshot wounds; kratom was detected incidentally in these cases. Case 2 involved a 20-year-old male subject found in the bed of a pickup truck where he had been sleeping with a small propane heater running all night. Autopsy examination revealed cherry red lividity and blood, and pulmonary edema; toxicology testing revealed a toxic blood carboxyhemoglobin saturation of 71%. Case 4's history and autopsy findings, including extreme cardiomegaly (930 g) and thrombosis of the left anterior descending coronary artery, were indicative of a cardiac death; the typical findings associated with opioid-related deaths, such as pulmonary edema, cerebral edema, and urinary retention, were absent. Case 5's autopsy examination and microbiological cultures of blood and lung revealed *Staphylococcus aureus* pneumonia and sepsis. While several substances including mitragynine were detected in blood, levels were interpreted as noncontributory, particularly given the clear anatomic cause of death. Regarding findings associated with opioid-related deaths, the lungs were mildly heavy (700 and 650 g) and exuded fluid at autopsy, but also were heavily involved by pneumonia, which is also consistent with these findings. The bladder was empty, and there was no cerebral edema. Case 6 involved a mildly obese man trapped face down in a tree well while skiing for an unknown downtime. Autopsy examination revealed cerebral and pulmonary edema associated with anoxic brain injury following resuscitation, multiple posterior left-sided rib fractures and thoracic spine transverse process fractures, abrasions and contusions of the anterior chest, and mild focal coronary artery atherosclerosis. The cause of death was asphyxia; contributory conditions were blunt head and torso trauma, hypothermia, and acute ethanol and mitragynine intoxication. The intoxication contributed to his death in that it likely made it more difficult to extricate himself from the tree well; it is unclear whether there was any direct physiologic contribution. Case 8's autopsy revealed atherosclerotic and hypertensive cardiovascular disease, with severe (up to 80%) narrowing of the 3 major coronary arteries, severe aortic atherosclerosis, and moderate arteriolonephrosclerosis. The lungs were hyperinflated with apical blebs and marked anthracotic

TABLE 1. Toxicology and Demographic Data From 27 Cases With Mitragynine Listed on the Death Certificate as Part of the Cause of Death or Under Contributory Conditions*

Case	Age, y/Sex	BMI, kg/m^2	Mitragynine, ng/mL	Opioids, ng/mL	Benzodiazepines, ng/mL	BAC, g/100 mL	Antidepressants, ng/mL	Other Drugs, ng/mL
1	28/Male	21.2	120	9.0 Codeine 100 Morphine 8.7 6-MAM		0.175		29 Cocaethylene 380 Benzoylecgonine
2	58/Female	44.6	470				1100 Venlafaxine 520 *O*-desmethylvenlafaxine	13,000 Levetiracetam 34 Amphetamine 560 Methamphetamine
3	76/Female	35.0	250	2300 Oxycodone 38 Tramadol	100 Diazepam 270 Nordiazepam		79 Paroxetine 30 Fluoxetine	14,000 Gabapentin 150 Zolpidem 1.6 11-Hydroxy delta-9 tetrahydrocannabinol (THC) 7.6 Delta-9 carboxy THC 0.5 Delta-9 THC (0.5) 200 Diphenhydramine
4	50/Male	24.2	950					310 Aripiprazole
5	47/Male	35.2	120	36 Morphine				160 Loperamide 510 Desmethyl loperamide
6	37/Male	54.5	1800	5400 Tramadol 380 *O*-desmethyltramadol (*O*-DSMT)			110 Venlafaxine 41 *O*-desmethylvenlafaxine	28,000 Gabapentin 1300 Topiramate
7	64/Male	23.1	450			0.128		13,000 Levetiracetam 170 Diphenhydramine
8	27/Male	27.3	88	33 Codeine 590 Morphine 25 6-MAM				14 Amphetamine (14) 230 Methamphetamine
9	38/Male	24.8	580					12,000 Gabapentin 63,000 Nitrous oxide 210 Doxylamine
10	42/Male	25.4	60	7.5 Fentanyl				
11	20/Male	23.8	67	19 Codeine 410 Morphine 5.2 6-MAM		0.015		22,000 Nitrous oxide
12	47/Male	N/A	170	18 Fentanyl	26 Alprazolam	0.183		58 Tadalafil (+) Quinine
13	42/Male	28.2	79	7.2 Hydrocodone	12 Alprazolam			0.53 Delta-9 THC 120 Amphetamine 940 Methamphetamine
14	28/Female	23.2	8.7	170 Oxycodone 11 Oxymorphone				22,000 Acetaminophen
15	31/Male	30.8	12	50 Oxycodone 23 Oxymorphone 5.9 Fentanyl 0.37 Norfentanyl	20 Diazepam 31 Nordiazepam 38 Alprazolam			2.3 11-Hydroxy delta-9 THC 59 Delta-9 carboxy THC 13 Delta-9 THC 29 Amphetamine

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TABLE 1. *(Continued)*

Case	Age, y/Sex	BMI, kg/m^2	Mitragynine, ng/mL	Opioids, ng/mL	Benzodiazepines, ng/mL	BAC, g/100 mL	Antidepressants, ng/mL	Other Drugs, ng/mL
16	56/Female	20.1	460	7.7 Dihydrocodeine 54 Hydrocodone			120 Bupropion 420 Hydroxybupropion 190 Fluoxetine 400 Norfluoxetine	180 Hydroxyzine
17	20/Male	31.3	42	16 Fentanyl 6.5 Norfentanyl	10 Flubromazolam			21 Cocaine 780 Benzoylecgonine
18	43/Male	29.0	490	120 Morphine 230 Oxycodone 7.7 Oxymorphone	670 Diazepam 750 Nordiazepam 70 Oxazepam 64 Temazepam 25 7-aminoclonazepam	0.014	100 Trazodone 510 Citalopram/ escitalopram	17,000 Acetaminophen 7000 Carisoprodol 3500 Meprobamate 54 Zolpidem 160 Diphenhydramine
19	48/Male	31.0	88	8.3 Dihydrocodeine 44 Morphine 47 Hydrocodone 1.0 6-MAM	130 Diazepam 150 Nordiazepam 6.0 Alprazolam 7.5 Etizolam	0.020	260 Citalopram/ escitalopram	21 Delta-9 THC
20	36/Male	31.5	440	39 Fentanyl 14 Norfentanyl		0.078		
21	30/Female	28.0	15	30 Morphine	25 Alprazolam		10,000 Doxepin 820 Desmethyldoxepin 180 Fluoxetine 160 Norfluoxetine 5800 Mirtazapine	2100 Diphenhydramine
22	35/Female	21.0	200				29 Desmethylsertraline	13,000 1,1-Difluoroethane
23	39/Male	36.0	100	10 Fentanyl 1.5 Norfentanyl				97 Zolpidem
24	41/Male	23.9	42	6.4 Codeine 30 Morphine	6.3 Lorazepam		51 Sertraline 71 Desmethylsertraline	210 Amphetamine 2400 Methamphetamine
25	32/Male	29.4	29	43 Codeine 720 Morphine 8.8 6-MAM		0.056		100 Amphetamine 280 Methamphetamine
26	36/Male	42.9	52	14 Codeine 260 Morphine 10 6-MAM		0.016		43 Amphetamine 260 Methamphetamine
27	38/Female	27.0	91	12 Codeine 470 Morphine 7 6-MAM				

TABLE 2. Toxicology and Demographic Data From 8 Cases Where Mitragynine Was Detected on Toxicology Testing But Not Listed as a Cause or Contributory Factor*

Case	Age, y/Sex	BMI, kg/m^2	Mitragynine, ng/mL	Opioids, ng/mL	Benzodiazepines, ng/mL	BAC, g/100 mL	Antidepressants, ng/mL	Other Drugs, ng/mL	Cause of Death
1	30/Male	23.1	130					130 Amphetamine 920 Methamphetamine	Gunshot wound of torso
2	20/Male	27.4	280			0.182		2.6 Delta-9 THC 95 MDA 71% sat Carboxyhemoglobin	Carbon monoxide poisoning
3	27/Male	21.4	110		23 Nordiazepam			2800 Butalbital 2.2 Delta-9 THC	Gun Gunshot wound of the head
4	43/Female	51.0	980					170 Diphenhydramine	Hypertension and atherosclerotic cardiovascular disease
5	36/Male	32.6	410	13 Dihydrocodeine 61 Hydrocodone			250 Fluoxetine 450 Norfluoxetine 65 Mirtazapine	8600 Acetaminophen 33 Delta-9 Carboxy THC 2.3 Delta-9 THC 440 Diphenhydramine	*S. aureus* sepsis
6	37/Male	31.5	110			0.180		2.2 11-hydroxy δ-9 THC 4.6 Delta-9 THC	Asphyxia
7	32/Male	24.4	390			0.271			Gunshot wound to the head
8	68/Male	24.6	110	5.9 Codeine 5.5 Buprenorphine 12 Norbuprenorphine	31 7-Aminoclonazepam			76 Diphenhydramine 670 Pseudoephedrine 13 Norpseudoephedrine	Atherosclerotic and hypertensive cardiovascular disease

*Caffeine, nicotine, cotinine, and naloxone found on toxicology were omitted from the tables.

BAC, blood alcohol concentration.

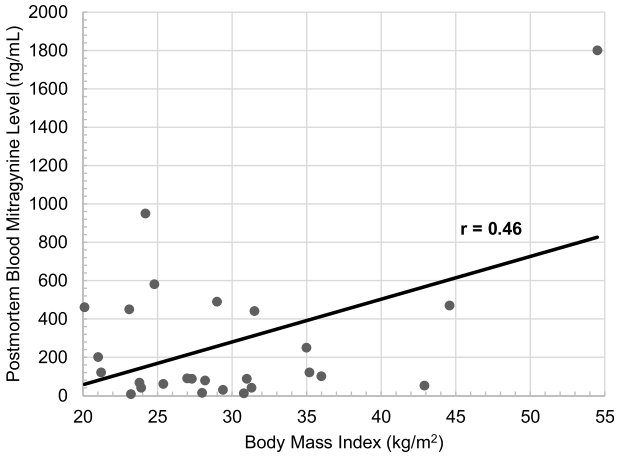

FIGURE 1. Correlation between BMI and mitragynine concentrations in postmortem blood samples from mitragynine-related cause of death cases (n = 26 [1 case was omitted because no BMI, height, or weight was obtained]).

discoloration consistent with the history of chronic obstructive pulmonary disease; there was no gross pneumonia or pulmonary edema. There was no cerebral edema or urinary retention. Toxicologic findings, including detection of mitragynine, were not thought to contribute to this apparent natural death.

The literature review revealed a wide range of mitragynine concentrations, 10 to 4800 ng/mL,[9–18] which is comparable to the slightly narrower range reported in this study, 8.7 to 1800 ng/mL. Our case where mitragynine was the sole intoxicant, 950 ng/mL, was in the middle of the concentrations found in other reported cases of sole mitragynine toxicity, 260 to 1900 ng/mL.[11,15] This wide range demonstrates why our *P* value (>0.201) was not statistically significant for the comparison of the 2 study groups (mitragynine-related fatalities and cases with incidental detection of mitragynine and an unrelated cause of death). The concentration at which mitragynine is found to be lethal varies widely because of the potential effects of agonal metabolism, additional cointoxicants, variations in individual metabolism, and opioid tolerance.

Agonal metabolism must be considered because of the potential for a long agonal comatose interval after irreversible brain damage has occurred (due to respiratory depression and cerebral anoxia) but before cardiac death. This is seen with some opioid-related deaths and can result in lower levels being detected in postmortem blood as the liver continues to function during the agonal period, potentially metabolizing the parent drug. Several central nervous system depressants were detected on toxicological analysis of both groups including opioids, benzodiazepines, and ethanol. Considering that mitragynine acts similarly to opioids at higher doses, when combined with other central nervous system depressants it could contribute to death at varying doses and blood concentrations due to the combined effects of multiple substances. Such additive lethal effects have been demonstrated with krypton, a mixture of mitragynine and *O*-desmethyltramadol (another μ-receptor agonist), in 9 accidental overdoses in Sweden.[14]

The components in kratom are known to act on a variety of receptors in the body and can enact opioid-like effects as well as stimulant-like effects at low doses. These mechanisms are not well known, but it has been shown that mitragynine acts as an agonist at the α2-adrenoceptors, as well as blocking stimulation of serotonergic 5-HT_{2A} receptors, which could lend to its stimulant-like effects.[4,20] Thus far, there has not been a clinical study on kratom and its effects, but there are many patient reports of the stimulant-like effects kratom provided at low doses, ranging from increased work productivity, sociable behavior, and euphoric effects to withdrawal symptoms upon cessation of the drug.[20,21] Adverse effects, such as tachycardia, agitation/irritability, and increased blood pressure, have also been associated with mitragynine use.[22–26] It is possible that, in addition to kratom's lethality related to opioid effects, it could contribute to other deaths such as cardiovascular ones by its stimulant effects. The potential sympathomimetic effects of mitragynine discovered during research for this project generally were not taken into account in the medical examiners' cause of death determinations in the cases we report here. More research is needed to determine whether the physiologic stimulant effects or possible arrhythmogenic potential of mitragynine may be as strong as effects seen with other forensically relevant sympathomimetics, such as cocaine and methamphetamine.

Mitragynine is a substance with intermediate lipophilicity, having a high penetration of the blood-brain barrier, which is thought to be responsible for some of its psychotropic effects.[27] The pharmacokinetics has been poorly studied in humans to date. The only study analyzing the pharmacokinetics in humans was conducted on 10 male regular users of kratom, using therapeutic doses. They reported linear pharmacokinetics that followed an oral 2-compartment model; the results of the study demonstrated an apparent volume of distribution (V_d) of 38.04 ± 24.32 L/kg, terminal half-life of 23.24 ± 16.07 hours, and a clearance of 1.40 ± 0.73 L/h.[26] Adipose tissue in the body acts as a reservoir for lipophilic drugs, and thus, the greater the quantity of adipose tissue, the greater the potential that mitragynine could be stored or redistributed. It has been shown that obese individuals have altered pharmacokinetics, an increased V_d and elimination half-life, of other lipophilic drugs that act at opioid receptors, such as fentanyl and sufentanil.[28] It has been recommended that the dosage of another lipophilic drug class, benzodiazepines, be increased based on total body weight when administered because of the increased V_d and elimination half-life in those who are obese.[29] Thus, we hypothesized that individuals with higher BMIs would have a higher distribution of mitragynine in tissues, potentially reflected in the concentrations detected on toxicology testing through postmortem redistribution.

The relationship with BMI is not straightforward, as evidenced by our Pearson correlation coefficient, $r = 0.46$. The concentrations varied widely between BMIs. For example, the case with the highest concentration, 1800 ng/mL, had a BMI of 54.5 kg/m^2, whereas another lethal case with a morbidly obese BMI, 42.9 kg/m^2, had a mitragynine concentration of only 52 ng/mL. In the case in which mitragynine was the sole intoxicant reported, the concentration was 950 ng/mL at a BMI of 24.2 kg/m^2. In another case, the concentration was comparable at 980 ng/mL, but the BMI was 51.0 kg/m^2. While the concentration in the first case resulted in death, it did not in the second case, which was ruled as a natural death from atherosclerotic and cardiovascular disease with an acute coronary artery thrombosis as a somewhat indisputable cause of death. These 2 cases may demonstrate the varying effects different concentrations may have on individuals with differences in metabolism. It is also worth noting that because mitragynine is lipophilic, blood concentrations may be particularly affected by postmortem redistribution in the obese because of high V_d and adipose reserves. It is apparent that while BMI may play a role in considerations around the metabolism of mitragynine, more research is needed to fully understand how individual variations in pharmacokinetics ultimately alter the effects of mitragynine.

Additionally, there is the potential for tolerance in chronic users, which may result in overlap in therapeutic and toxic ranges, similar to other opioids. It also has been noted that mitragynine is metabolized to more potent alkaloids such as 7-HMG and pseudoindoxyl.[3] Currently, these additional active metabolites

TABLE 3. Toxicology and Demographic Data From 10 Literature Articles Where Mitragynine Was Detected on Toxicology Testing

Source	Age, y/Sex	COD	Mitragynine, ng/mL	Opioids, ng/mL	Benzodiazepines, ng/mL	BAC, g/100 mL	Antidepressants, ng/mL	Other Drugs, ng/mL
9		Aspiration of chyme	790		280 Etizolam 6.9 Lorazepam 1.1 Triazolam		89 Fluoxetine	3000 Pregabalin 7.4 Pipamperone 18 Quetiapine 5.8 Olanzapine 5.2 Methylmethcathinone
9		Mixed drug toxicity	10	210 Morphine 41 6-MAM 24 Codeine			480 Hydroxybutyrates	34 Amphetamine 40 MDA 3300 Methamphetamine 1400 MDMA 8 Pseudoephedrine 1900 Paracetamol
10	Male	Apparent seizure leading to cardiorespiratory arrest	(+)					
10	Male		16			0.018	1.3 Etizolam	56.19 5-MeO-AMT (+) Acetaminophen (+) Gabapentin
10	Male		170				(+) Selegiline	157 1,3-dimethylamylamine, methylhexanamine
10	Male		4800					2.83 Trimethoxyamphetamine (+) Inhaled hydrocarbons
10			(+)	19 Butryl-fentanyl oxycodone 48	(+) Etizolam			68 Diphenhydramine 1.7 THC
10			(+)	U-47700 mass spec signature present				
10			890				320 Fluoxetine	990 Pseudo-ephedrine
10			(+)	220 Morphine 17 Codeine				
10		Probable mechanical asphyxia accompanied by mixed drug intoxication	140	(+) Oxycodone (+) Tramadol				<200 Topiramate <50 Diphenhydramine (+) Zolpidem
10			2100				263 Citalopram	
10			1400	140 Furanyl-fentanyl				
10			1000		20 Temazepam 3.5 Clonazepam		400 Sertraline	27 Olanzapine 8.4 THC 110 Hydroxyzine
10			2700		110 Etizolam 53 Nordiazepam		31 Mirtazapine	
10			250	300 Oxycodone		0.252		
10			747	274 Oxycodone (+) Fentanyl		0.175		(+) Cocaine
11		Mitragynine toxicity	260					
11		Mitragynine toxicity	1400					

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TABLE 3. *(Continued)*

Source	Age, y/Sex	COD	Mitragynine, ng/mL	Opioids, ng/mL	Benzodiazepines, ng/mL	BAC, g/100 mL	Antidepressants, ng/mL	Other Drugs, ng/mL
11		Mitragynine and ethanol toxicity	200			0.181		
11		Mixed drug toxicity	540		(+) Clonazepam			(+) Cocaine
12	20/Male		390	<50 Morphine				1700 Propylhexedrine <50 Promethazine <5000 Acetaminophen
13	Male	Mitragynine toxicity	1060				360 Citalopram	43 Zopiclone 5.4 Lamotrigine 150 7-HMG
14	22/Male	Accidental drug toxicity	70		0.14 Alprazolam	0.09	0.4 *O*-desmethyltramadol	
14	35/Male	Accidental drug toxicity	160				0.7 *O*-desmethyltramadol 0.1 Desmethylalimemazine 0.7 Venlafaxine 0.1 *O*-desmethylvenlafaxine	0.3 Alimemazine
14	30/Female	Accidental drug toxicity	40		0.3 Diazepam 0.3 Nordiazepam		0.5 *O*-desmethyltramadol 0.6 Fluoxetine 0.5 Norfluoxetine	19.8 Phenazon 0.2 Olanzapine 5.0 Pregabalin 0.04 Amphetamine
14	33/Male	Accidental Drug Toxicity	50		0.05 Nordiazepam		1.5 *O*-desmethyltramadol 0.2 Desmethylalimemazine	0.2 Alimemazine 0.1 Olanzapine 0.002 THC
14	27/Male	Accidental drug toxicity	180	0.0004 Buprenorphine			4.3 *O*-desmethyltramadol 0.1 Mirtazapine 0.1 Venlafaxine 0.09 Diazepam 0.2 Nordiazepam	0.2 Alimemazine
14	27/Male	Accidental drug toxicity	50			0.01	1.2 *O*-desmethyltramadol	0.04 Zopiclone
14	24/Male	Accidental drug toxicity	30				1.1 *O*-desmethyltramadol 0.14 Alprazolam	0.20 Amphetamine 0.0006 THC
14	25/Female	Accidental drug toxicity	20				0.8 *O*-desmethyltramadol 1.0 Venlafaxine 1.1 *O*-desmethylvenlafaxine	0.06 Zopiclone
14	32/Male	Accidental drug toxicity	50				1.1 *O*-desmethyltramadol 1.2 0.8 Citalopram 1.3 0.07 Alprazolam	0.007 THC
15	33/Male	Mitragynine toxicity	1900					2.6 THC
16	24/Male	Mixed drug toxicity	230			0.02	1100 Venlafaxine 1600 *O*-desmethylvenlafaxine 240 Mirtazapine	450 Diphenhydramine
17	17/Male	Accident	600		210 Temazepam 210 7-Amino-clonazepam			280 Dextromethorphan 330 Diphenhydramine
18	56/Female	Accident; multidrug toxicity	2500	190 Oxycodone	63 Lorazepam			

*Caffeine, nicotine, cotinine, and naloxone found on toxicology were omitted from the tables.

of kratom are not routinely included in toxicology panels in the medical examiner setting; they should be included so that a more comprehensive analysis of the true lethal levels of compounds comprising kratom's effects may be conducted.

Based on the number of deaths attributed solely to kratom, this drug should be evaluated for safety and efficacy and regulated. This opioid extract has not been subject to clinical trials, and furthermore, marketed kratom products are not controlled or standardized for extract potency. Furthermore, it is unclear whether its stimulant effects at low doses could play a contributory role in the death of individuals with cardiac disease, or potentially be sufficient even to cause cardiac arrhythmia without underlying heart disease. Until this drug is regulated and standardized, and access to it controlled, deaths due to its effects will continue. It remains to be seen whether any therapeutic application of the compounds comprising kratom is possible.

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