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KRATOM (O GRUNDMANN AND K SMITH, SECTION EDITORS)

What Is the Kratom Overdose Risk? A Systematic Literature Review

Corneliu N. Stanciu[1] · Samantha A. Gnanasegaram[2] · Gerald L. Rader III[1] · Abhisheak Sharma[3] · Christopher R. McCurdy[4]

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Abstract

Purpose of Review The rising public interest in kratom is paralleled by concerns of adverse outcomes, particularly overdose. Such claims span a multitude of reporting modalities, including case reports, analyses of data from poison control and coroners' reports, and warnings from government agencies. Here we evaluate the literature in efforts to assess kratom's potential overdose risk. A keyword search of online literature databases identified 12 preclinical studies, 23 case reports, and 15 observational studies/reports meeting our pre-selected criteria.

Recent Findings Case reports describe outcomes where kratom products are coingested with illicit substances and pharmaceuticals. Opioids are common coingestants, and presentations describe pulmonary edema and findings resembling opioid overdoses. However, seizures and hyperadrenergic features are also common. Where reported, post-mortem mitragynine (MG) concentrations are inconclusive of attributed toxicities. Animal studies found oral LD_{50s} in the range of 200–960 mg/kg for MG, and 200–591 mg/kg for Malaysian total alkaloid extract. Deaths were preceded by restlessness, tremors, and convulsions. Analyses of a variety of reported toxicities yield signs and symptoms that resemble hyperadrenergic components, with autopsies finding coingestants in addition to alkaloids.

Summary As with any compound ingested in large quantities, it is possible to develop lethal toxicities with kratom in a dose-dependent fashion. Use via the traditional mode of consumption, such as chewing or brewing the leaves as a tea, would require a tremendous amount of kratom to be ingested. The currently available kratom products, and pure alkaloid isolates, greatly increase this risk, in addition to combining kratom with illicit substances, and pharmacokinetic/pharmacodynamic interactions.

Keywords Kratom · *Mitragyna speciosa* · Mitragynine · 7-hydroxymitragynine · Overdose · Opioid

Introduction

Kratom (*Mitragyna speciosa* Korth) is an evergreen tree from the coffee family, Rubiaceae, native to Southeast Asia. For centuries, its leaves have been used for various remedies, to assist with pain management, enhance endurance, and as part of traditions and ritual ceremonies [1]. Typical consumption modalities involve either chewing the leaves or brewing them as a tea, or, to a lesser degree, smoking them [1]. Indigenous people do not regard it as "drug use," but, rather, as a way of life, embedding it in traditions and customs similar to the Western coffee consumption. In its native setting, the use of kratom is considered safe, and reports of significant adverse effects or mortality in Asia are not extensively documented [1].

In time, it has also gained popularity as an opioid substitute to ameliorate opioid withdrawal symptoms and aid

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✉ Corneliu N. Stanciu
Corneliu.N.Stanciu@hitchcock.org

[1] Department of Psychiatry, Dartmouth-Hitchcock Medical Center, Dartmouth's Geisel School of Medicine, One Medical Center Dr., Lebanon, NH 03756, USA

[2] Hope Counseling Services, 14 Leavitt Rd, Pittsfield, NH 03263, USA

[3] UF Translational Drug Development Core, Department of Pharmaceutics, University of Florida, Gainesville, FL, USA

[4] UF Translational Drug Development Core, Department of Medicinal Chemistry, College of Pharmacy, University of Florida, Gainesville, FL, USA

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in abstinence [2]. Its potential for tolerance, dependence, and addiction in some users has long been apparent, leading to its criminalization in Malaysia and, until recently, also, Thailand where it is one of the most used drugs with a prevalence ranging from 2.9 to 12% among the population [3, 4]. A recent trend in the region has been its use in urban settings by young individuals as part of polydrug concoctions for euphoric effects [5].

Since 2015, use of kratom has sharply increased in popularity in the USA for reasons including self-management of opioid use disorder symptoms, pain, focus and concentration, as well as mood and anxiety states [6, 7]. Correlational analyses support a greater burden of mental health and substance use disorders, especially opioids, among users [8]. Based on import data, there are close to 16 million users in the USA [9], although prevalence estimates of regular users specifically are unknown. Unlike traditional modalities of kratom use, products available in the USA are diverse in terms of content, dosage forms, potency, marketing, lack regulatory control [10]. Such products are made from powdered dry leaves or concentrated extracts and formulated into tablets, capsules, powders, liquids, and other preparations. These products are readily available for purchase in gas stations, local head shops, and online.

In recent years, paralleled by the increases in importation of raw materials, sales, and use, there have also been a growing number of reports of adverse outcomes as well as increasing concerns over overdoses and fatalities. As of 2022, kratom is not scheduled as a controlled substance in the USA; however, government agencies have taken a number of actions including issuing public health advisories and import alerts [11]. In 2018, the US Food and Drug Administration (FDA) cited 44 cases of kratom-associated deaths based on coroner or forensic toxicology reports [12], and, subsequently, the DEA listed it as a drug of concern.

Kratom is a complex botanical comprising of over 40 alkaloid constituents. The two most studied are mitragynine (MG) and 7-hydroxymitragynine (7OHMG), the first acting on multiple receptor systems. Although the FDA conducted a computational study concluding that several alkaloids bind to opioid receptors [13], pharmacodynamic effects cannot be inferred. At these receptors, both MG and 7OHMG act through G-protein-coupled signaling. At the mu opioid receptor (MOR), MG has a much lower affinity compared to morphine, whereas 7OHMG has much higher affinity than both [14, 15]. Pharmacodynamic studies have found that, at human MOR, 7OHMG displays high efficacy partial agonism, while MG exerts both antagonistic and agonistic activities, depending on the MOR efficacy required [14, 15]. Emerging evidence favors biased partial agonism, where MG-induced MOR activity leads to G-protein activation; however, unlike with traditional opioids, it does not recruit the β-arrestin pathway, which is thought to be involved in respiratory depression, constipation, tolerance, cross-tolerance to morphine, and other undesirable opioid effects [16].

In addition to other receptor systems, MG also stimulates α_2 adrenergic receptors accentuating its sedative, hypnotic, and analgesic effects, without causing respiratory depression [17]. This synergistic profile translates into the benefits noted by people using kratom to manage opioid withdrawal; however, it can yield potent CNS depressant effects, and it is dangerous when combined with other sedative agents such as opioids, alcohol, and benzodiazepines. Despite the foreseeable adverse effects from co-ingestion of kratom with illicit substances and pharmaceuticals, a gap exists in our understanding of the risk of overdosing on kratom and the associated clinical presentation. In this systematic review, we evaluate all available levels of evidence concerning the overdose potential of kratom.

Methodology

Data Sources

We searched PubMed/MEDLINE, PsycINFO, PsycARTICLES, CINAHL, EMBASE, Scopus, Cochrane, and Academic OneFile for all English-language medical literature published between January 1, 1970 and August 1, 2022 using the search terms: “mitragyn + death”; “mitragyn + overdose” ; “mitragyn + toxic*”; “kratom + death” ; “kratom + overdose” ; “kratom + toxic*.”

Search results were supplemented by references gleaned from recent reviews and citations of searched returns.

Inclusion and Exclusion Criteria

All studies reporting outcomes of kratom or kratom constituent exposure in the context of lethal or near-lethal outcomes were considered. Human, animal, and in vitro studies were included. Any formulation and administration route were accepted. The original search yielded 521 reports. C.S. and S.G. examined each by title and abstract. After eliminating studies with exclusionary criteria, 50 papers met our original search criteria. Figure 1 depicts a flow diagram describing study selection. Disagreements in whether a report was eligible for the study would have been mediated for proper allocation by a third reviewer, but no studies required mediation.

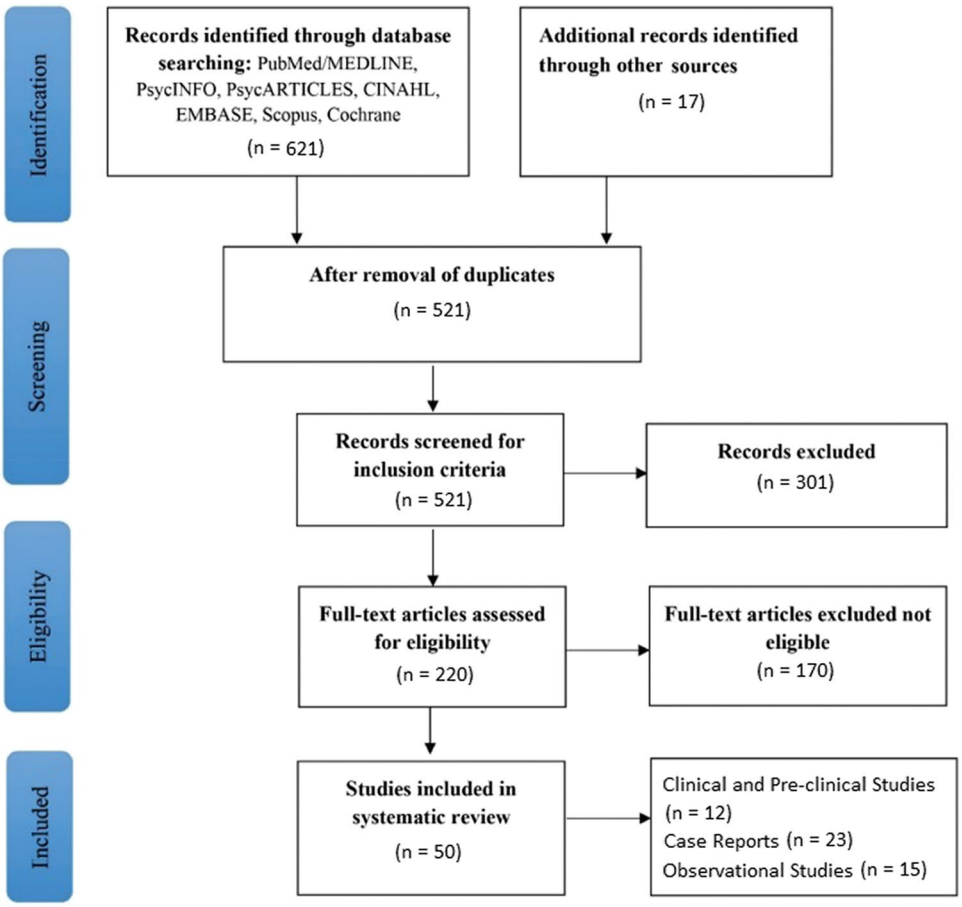

Fig. 1 Flow diagram depicting study selection

Results

Case Reports

A total of 23 case reports described the fatal and near-fatal outcomes of 18 males and 5 female patients [18–39]. A summary of these reports is found in Table 1.

All fatalities involved opioids and other illicits, as well as prescription pharmaceuticals. One report described a patient who committed suicide by hanging and had kratom in his possession at the time of death. Several cases reported quantitative MG levels in urine or blood, measured by a variety of laboratory techniques. Autopsies were mostly consistent with opioid-like toxicities (pulmonary congestion, cerebral edema, and urinary retention). There were also some instances where substances other than MG were determined insufficient to have caused the death alone, and, here, MG levels of 230, 600, 1060, and 1900 ng/mL were reported. None of these cases specified the time frame from specimen collection to laboratory testing. Conversely, there were also cases reporting MG concentrations as high as 2500 ng/mL; however, kratom was not deemed as the cause of death. Of near fatal cases, the majority documented various hyperadrenergic outcomes such as nausea, vomiting, restlessness, palpitations, acute kidney injury, and rhabdomyolysis due to vasoconstriction, and seizures. Where specified, respiratory rate and oxygen saturations were within normal limits, although one case report documented a decreased respiratory rate, which improved with naloxone administration.

Clinical and Pre-clinical Studies

There are no human trials assessing kratom's toxicity. There are ten in vivo (mice, rats), one in vitro (human cell lines), and one study that evaluated both in vitro (brine shrimp) and in vivo (rats) aspects of various preparations of kratom (extracts, MG, and individual alkaloids)-administered PO, IV, and IP. A summary can be found in Table 2. Some studies specifically aimed to assess acute, or subacute, toxicity, whereas others reported toxic lethal outcomes as a secondary, or indirect, finding.

Seven studies reported on LD_{50} values, the statistically derived amount of a substance that can be expected to cause death in 50% of the animals when given via a specific route as a single dose and then observed for a specified amount of time. With oral administration of total alkaloid extracts, LD_{50s} of 591 [40] and 200 mg/kg [41] were reported in Malaysian studies, and 173 mg/kg in a Thai

Table 1 A summary of case reports included in this review

Case	Subject	Context	Presentation	Investigations	Respiration /Saturation	MG (ng/mL)	Comments
Tobarran 2022	31-yo M with h/o substance use	Presented to ED after loss of consciousness for 6 h after smoking kratom	Rhabdomyolysis, acute renal and hepatic injury, electrolyte disturbances, progressed to compartment syndrome over ~ 3 h and required fasciotomy with 18-day ICU admission	BAL negative, UDS negative		500 (serum), 600 (urine)	
Sangani 2021	45-yo F h/o breast cancer, Crohns dz, pain	Passed out at home after ingesting ~ 12 capsules of kratom product, which she initiated 1 mo ago and increased use over the last 2 wks	Decreased hearing, R lower extremity swelling and pain (compartment syndrome). Required multiple interventions for rhabdomyolysis, debridement, dialysis due to AKI	UDS negative, Cr, 1.72; WBC, 28.6; K, 6.5; AST, 509; ALT, 155; Alk Phos, 345; CPK > 24,156			Alpha adrenergic stimulation presumed to have led to vasoconstriction.
Singh 2020	62-yo F with h/o COPD and asthma	Presented to ED after ingesting kratom for pain for the first time	Nausea, vomiting, and abdominal cramping	WBC 11600, CBC WNL, BUN 22 mg/dL, BMP WNL, LFTs, and Lipase WNL	16 BPM / 97%		Treated with IV ondansetron, IV promethazine, and normal saline infusions.
Wong 2020	15-yo F	A suicide attempt by an overdose on 45 capsules of 500 mg each of kratom product	Dry mouth, dizziness, nausea and vomiting, restlessness, and palpitations	UDS negative, HR 100BPM, miotic pupils, bilateral upper extremity tremors. K 2.9, lactic acid 3.2. EKG tachycardia, QTc 474			
Matson 2019	33-yo M h/o heroin addiction, anxiety, depression, and polysubstance abuse	Found unresponsive, PEA multiple CPR attempts by EMS. Last received vivitrol 10 mo ago.	PEA	ELISA, GC neg, LC/MS = delta THC 0.0026 mg/L, cotinine and MG 1.9 mg/L. Pulmonary congestion and edema seen in an opioid overdose		1,900 (blood)	Only case where kratom alone was involved (along with THC, cotinine).

Table 1 (continued)

Case	Subject	Context	Presentation	Investigations	Respiration /Saturation	MG (ng/mL)	Comments
Shekar 2019	36-yo M	Presented to ED intubated by EMS after being found down for an unknown amount of time at home. Naloxone administered in the field.	GCS 3, pinpoint pupils, HR 130 BPM, BP 80/40	AST 1347, ALT 3717, hyperkalemia, AKI, Anion gap 18, lactic acid 7.1 mmol/L, CK 700 U/L; urine and blood toxicology, negative			Urine 7OHMG > 5.0 mg/L
Aggarwal 2018	26-yo M	Brought to ED in cardiorespiratory arrest with history of unknown amount of kratom ingestion 24 h prior; ROSC achieved after 1 h but subsequently died 12 h later due to worsening cardiorespiratory function	Primarily PEA with a brief period of ventricular arrhythmia	CT scan immediately following ROSC showed imminent cerebral herniation, UDS + for codeine only which patient had taken shortly before admission (standard dose)			Intralipid administered which improved condition for a brief period.
Hughes 2018	27-yo M with h/o bipolar disorder, ASD (Asperger), and substance abuse	Found deceased at home with multiple prescription medications and a metal vaporizer beside him.	Intramuscular hemorrhage of tongue identified on autopsy.	On autopsy: valproic acid was quantitatively 8.8 mcg/mL, quetiapine 12000 ng/ml, and MG was qualitatively positive.			Cause of death was ruled as acute toxic effects of quetiapine complicated by MG use.
Wang 2018	56-yo F with h/o COPD, prescribed oxycodone and lorazepam, also known to use CBD oil and reportedly ingesting a “methadone-like” powder from Indonesia	Found dead in bed after recent complaints of dyspnea and cough		Full autopsy performed; femoral venous blood toxicology showed oxycodone, lorazepam, and MG		2,500 (femoral blood)	The "measured MG is likely independently fatal".
Diep 2017	24-yo M with ASD (Asperger), depression, substance abuse	Found down and minimally responsive, history of recent suicidal ideation, alcohol use, and kratom use per history	Hypothermic (94.8°F), seizure witnessed by EMS for which lorazepam was administered	UDS, negative; ABG showed acute respiratory acidosis; QTc 492; HR 58 BPM; WBC 19000; CK 1342 U/L; CT head, negative			Discharged from inpatient psychiatry to residential substance use treatment; started on buprenorphine for control of kratom cravings

Table 1 (continued)

Case	Subject	Context	Presentation	Investigations	Respiration /Saturation	MG (ng/mL)	Comments
Domingo 2015 #1	22-yo M h/o psychosis, anxiety, and substance abuse	Found dead in bed morning after consuming an "herbal" mixture; also fell from a 1st-story window after consuming mixture and before going to bed		Toxicology also found Etizolam , pregabalin, lorazepam, triazolam, quetiapine, olanzapine.		790 (femoral blood)	
Domingo 2016 #2	20-yo M h/o autism	Found dead with kratom and other paraphernalia at the scene		Toxicology also found methamphetamine, amphetamine, codeine, morphine.		10 (femoral blood)	Mixed drug intoxication with heroin, methamphetamine, MDMA, GHB
Mcintyre 2015	24-yo M h/o multiple prior suicide attempts as well as "alcohol abuse and depression"	Found dead in bed of "friend" after drinking "one glass of wine and a beer" then taking a "sleeping pill"		On autopsy: pulmonary edema and congestion, moderate urinary retention, urine and blood toxicology		230 (peripheral blood)	Therapeutic levels of venlafaxine, mirtazapine, diphenhydramine also present on toxicology; BAL 0.02 mg/L
Karinen 2014	A "middle-aged man" with h/o substance abuse and "psychiatric disease"	Had purchased kratom online in order to avoid positive UDS at work		On autopsy 3 days postmortem: patchy areas of bronchopneumonia, lungs were congested and edematous, and urine and blood toxicology was also performed.		1,060 (femoral blood); 3,470 (urine)	Toxicology also revealed zopiclone, lamotrigine, and citalopram at therapuetic levels. 7OHMG = 0.15 mg/L (femoral blood) and 2.20 (urine).
Neerman 2013	17-yo M with h/o heroin use, chronic pain, depression and past suicide attempts	Found unresponsive, declared dead, ingested something the night before. A bag of kratom pills, a liquid and empty bottle of promethazine found.		Pulmonary congestion, edema. LC/TMS, several: dextromethorphan, diphendydramine, temazepam, 7-amino clonazepam and MG		600 (femoral blood)	

Table 1 (continued)

Case	Subject	Context	Presentation	Investigations	Respiration /Saturation	MG (ng/mL)	Comments
Holler 2011	20-yo M with no past medical or psychiatric history	Found dead "under his bunk" in his living quarters. Thirty-nine separate nutritional supplements, herbal supplements, and prescription and nonprescription medications were found at the scene. Propylhexidrine and mitragynine	On autopsy: bilateral pulmonary edema and bilateral pleural effusions	Urine immunoassay positive for amphetamines but negative on confirmation; blood and urine ethanol, negative; morphine present in urine but not in blood; promethzine, propylhexidine, and MG were also detected in urine.		390 (heart blood); 1200 (urine)	Also reported tissue concentrations in various organs; Propylhexedrine 1,700.
Nelsen 2010	64-yo M with h/o chronic pain and depression; prescribed amitriptyline and oxycodone	Found at home unconscious and seizing; known to have consumed a tea made with kratom and *Datura stramonium* approximately shortly prior	Decorticate movement of upper extremities, GCS of 6; HR, 110 BPM; BP, 143/70; RR, 14 BPM	Sinus tachycardia on EKG; UDS, positive for cannabinoids, tricyclics, and oxycodone	99% on RA	167 (urine)	
Tungtananuwat 2010	21-yo M	Found down on floor unconscious and not breathing	Bloody exudates from the nose and foamy blood from his mouth	Full autopsy not performed due to religious reasons; MG, caffeine, diphenhydramine, alprazolam, nortriptyline, methadone, tramadol, methamphetamine, and some of their metabolites were found after blood and urine analysis.			Presumed to be on OD of "4x100" (mixture of primarily kratom, cola, and codeine/diphenhydramine cough syrup)
Roche 2008	32-yo M with Chrohns and depression	Found having seizure-like movements and foaming at the mouth after using a kratom product purchased on the Internet.	Unresponsive, required intubation for 24 h. He developed fever, aspiration PNA, and hypotension.	Head CT, EEG wnl, all other laboratories wnl on presentation to ED. UDS, negative.			Not a fatal case. He was on Prozac. Seizure-like movement persisted despite benzodiazepines, intubation.

Table 1 (continued)

Case	Subject	Context	Presentation	Investigations	Respiration /Saturation	MG (ng/mL)	Comments
Overbeek 2019	39-yo F with depression and polysubstance abuse	Presented to the ED with altered mental status and a decreased respiratory rate	Obtunded with minimal responsiveness to painful stimuli. Also experiencing respiratory depression with bradypnea. She received two doses of 0.4 mg of naloxone.	Following administration, the patient's depressed mental status resolved and respiratory rate increased. She subsequently became acutely agitated, requiring haloperidol for sedation. She was monitored in the ED, receiving supportive care and intravenous fluids.			GC/MS analysis of her urine during was positive only for the presence of kratom and did not show other opioids.
Mowry 2013	36-yo M with depression, polysubstance abuse, and pasty suicidality	Generalized tonic-clonic seizure (found down at home by family) with empty bottles of lamotrigine, paroxetine, and an empty packet labeled "Da Pimp Bomb" with ingredients described as pure kratom. EMS found the patient pulseless and apneic, intubated him, and initiated ~30 min of CPR in the field. The patient received epinephrine and naloxone en route.	Physical exam: after return of spontaneous circulation: unresponsive on ventilator; BP, 106/63; HR, 118BPM; T, 34.3°C. Pupils dilated but sluggishly reactive, heart tachycardic, lungs with coarse breath sounds; abdomen, soft and nontender; GCS 3T with 1 + reflexes bilaterally and no clonus.	Autopsy findings: marked cerebral edema consistent with anoxic brain injury, with multifocal brainstem hemorrhage, multiple small recent pulmonary infarcts and pulmonary emboli, and recent thrombosis in prosthetic venous plexus. Laboratory testing showed a qualitative positive screen for MG and 7OHMG.	96%		Acute MG, paroxetine and lamotrigine ingestion. Cause of death was severe hypoxic encephalopathy complicating apparent MG toxicity.

Table 1 (continued)

Case	Subject	Context	Presentation	Investigations	Respiration /Saturation	MG (ng/mL)	Comments
Frank 2017	28-yo M	Found deceased in his residence with marijuana products and bags that contained green powders labeled "THAI" and "GREEN MAENG DA" and an unlabeled plastic bag that contained a crystalline white powder.		Autopsy findings included pulmonary and cerebral edema, urinary retention, and severe constipation.		1,400 (femoral blood)	Mixed drug intoxication of furanylfentanyl and mitragynine; Furanylfentanyl 140
Ramoo 2017	29-yo M h/o drug and alcohol abuse.	Found in a semi-seated position while partially suspended by a ligature with a package of kratom pills beside him.		EtOH, 83 mg/dL		980 (subclavian blood)	Asphyxia due to hanging, a suicide.

yo = years old; *M* = male; *F* = female; *h/o* = history of; *dz* = disease; *h* = hour; *wk* = week; *mo* = month; *PEA* = pulseless electrical activity

Table 2 A summary of pre-clinical studies included in this review

Study	Type	Aim	Subjects	Intervention	Alkaloid dose and route	Findings	Comments
Smith 2019	In vivo	Determine the PO and IV LD50 for MG and 7OHMG, and compare them to heroin	Swiss Webster male mice	Administered MG, 7OHMG and heroin in various doses, IV and PO	Retro-orbital IV injection of MG (62, 31, 25, 15, and 8 mg/kg) and 7OHMG (50, 25, 12.5, and 6.25 mg/kg). PO administration of MG (500, 250, 125, and 62.5 mg/kg) and 7OHMG (50, 25, 12.5, and 6.25 mg/kg)	IV LD50 of 27.8 (MG), 24.7 (7OHMG) and 23.7 (heroin) mg/kg. PO LD50 of 547.7 (MG) whereas none could be determined for 7OHMG in the 6.25 to 50 mg/Kg range.	Mice expired within first 10min from respiratory depression with IV. At high doses seizures do occur at 20min for those surviving. Also although no deaths were observed, respiratory depression and seizures were observed in mice receiving PO 7OHMG
Sabetghadam 2013	In vivo	Determine the dose–response relationship, ED50 and LD50 values, as well as the TI, for total alkaloid extract as well as MG and compare them to morphine.	Swiss Albino male mice	Administered an alkaloid extract as well as MG in various doses PO.	PO administration of alkaloid extract (20–400 mg/kg) and MG (4.2–84 mg/kg)	PO LD50 of 591 (alkaloid extract) and 477 (MG) mg/kg. The TI for MG (21:1) was wider than that of the extract (3:1).	Malayasian kratom, 12–20% MG Death was preceded by restlessness, perioral tremor, and generalized convulsion MG seems relatively safer when compared with the alkaloid extract however analgesics such as morphine have safer TI of 70:1 while cocaine and ethyl alcohol are 15:1 and 10:1 respectively
Macko 1972	In vivo	Determine acute and subacute toxicity of MG	Male rats	Administered MG PO.	A single PO dose of 525 and 807 mg/kg MG	PO MG LD50 960 mg/kg	In dogs, PO doses of up to 80 mg/kg and IV doses of up to 9.2mg/kg MG were tolerated well. Clonic convulsions, respiratory depression, panting and prostration, occurred following 31.8 mg/kg IV
Watanabe 1992	In vivo			Administered MG IP.		IP MG LD50 126.7 mg/kg	

Table 2 (continued)

Study	Type	Aim	Subjects	Intervention	Alkaloid dose and route	Findings	Comments
Saidin 2008	In vitro	Investigate cytotoxicity of MG and alkaloid extract using human somatic and cancer cell lines.	Cell lines	Administered MG to cells	Various doses administered to a cell cultured in ug/mL concentrations.	Cell proliferation inhibited at >100 µg/mL and cell death occurred at 1000 µg/mL	
Moklas 2008	In vitro and in vivo	Evaluate the toxicity level of MG using a brine shrimp lethality assay	Brine shrimp; male Sprague Dawley rats	Administered MG and alkaloid extract to brine shrimp (for lethality assay) and rats (for locomotor assay)	A single dose of MG at 1.0, 5.0, 10.0, and 30.0 mg/kg	MG (LC50 = 44 µL mL) had higher toxicity when compared with the alkaloid extract (LC50 = 62 µL/mL) in a brine shrimp test.	MG was found to be toxic to brine shrimp at 44µl/ml, with alkaloid extract (62 µl/ml) and aqueous extracts (98µl/ml) respectively. MG at both lowest and highest dose significantly reduced locomotor activity in rats suggesting sedative properties
Reanmongkol 2007	In vivo	Investigate the potential analgesic activities of the methanol and alkaloid extracts from kratom by using a hot plate test in mice and a tail flick test in rats	Male Swiss mice and Wistar rats	Administered extracts in incremental doses, depending on the previous outcome for each animal.	PO administration of methanol extract (50, 100, 200 mg/kg) and alkaloid extract (5, 10, 20 mg/kg PO)	PO LD50 of 173.2 mg/kg p.o. for alkaloid extract and of 4.90 g/kg for the methanol extract	Thailand kratom, 66% MG Signs of toxicity included lethargy, tremor, fatigue, paralysis, loss of righting reflex, apnea, tonic-clonic convulsion and death Doses used here are comparable to human daily consumption.

Table 2 (continued)

Study	Type	Aim	Subjects	Intervention	Alkaloid dose and route	Findings	Comments
Harizal 2010	In vivo	Identify acute toxicity effects including death related to administration of alkaloid extract	Sprague–Dawley male rats	Administered alkaloid extract while the control group received 430 mg/kg PO morphine. All animals were sacrificed after 14 days of treatment. Eight parameters were tested to evaluate signs of toxicity: cage side observation, body weight measurement, food and water consumption, blood pressure, absolute and relative organ weight, hematology, biochemical analysis and histopathology.	PO administration of alkaloid extract (100, 500, and 1000 mg/kg)	No mortality was noted after 14 days of treatment. Behavior, food and water consumption, hematological studies and organ weights showed no significant changes. Blood pressure was increased however after an hour with all doses. The highest dose of extract also induced acute severe hepatotoxicity and mild nephrotoxicity.	Malayasian kratom used (20-22% MG) Nephrotoxicity (elevated Cr) was seen only at a dose of 1000 mg/kg. Histological examination showed congestion of sinusoids, hemorrhage hepatocytes, fatty change, centrilobular necrosis and increased number of Kuppfer cells in the liver of all methanol extract treated groups.
Hill 2022	In vivo	Evaluate respiratory depressant effect of MG and 7OHMG	Male CD-1 mice	Incrementally administered PO MG, 7OHMG while respiration measured in freely moving mice using plethysmography chambers. The mice were also pre-treated with ketoconazole to inhibit CYP3A.	PO 7OHMG and MG in doses of 3–30mg/kg. Additionally, treated mice with ketoconazole	Morphine (3–30 mg/kg) and 7OHMG (3–30 mg/kg) dose-dependently depressed MV. Low dose MG (3 mg/kg) did not produce significant changes in respiration. MG at 10 mg/kg induced significant and prolonged respiratory depression that was not further increased at higher doses (30 and 90 mg/kg) Pretreatment with ketoconazole significantly reduced MG-induced respiratory depression however not 7OHMG	MG and 7OHMG induced respiratory depression, but only MG showed a ceiling effectwhich is due to metabolic saturation of CYP3A enzyme.

Table 2 (continued)

Study	Type	Aim	Subjects	Intervention	Alkaloid dose and route	Findings	Comments
Kamal 2012	In vivo	Evaluate acute toxicity of Malaysian aqueous extract	Sprague Dawley rats, both male and female	Administered various doses of the extract.	PO administration of 175, 500, and 2000 mg/kg for 14 days	No mortality, so estimate that the LD50 value was higher than 2000 mg/kg	Human consumption is aquaous extract (boiling). Histological examination showed steatosis and centrilobular necrosis only on several parts of the liver
Azizi 2010	In vivo	Investigate the effects of different extracts on glutathione transferase-specific activity	Male Sprague Dawley rats	Various interventions	PO administration of alkaloid extract	200 mg/kg PO of Malayasian total alkaloid extract led to death in the preliminary study	Not the aim of the study however they found lethality with 200mg/kg PO.
Janchawee 2007	In vivo	Assess a laboratory calibration method	Male rats	Administered a one-time dose of MG	PO administration of MG	200 mg/kg PO led to death	

study [42]. Studies evaluating pure MG found LD_{50s} of 200 [43], 477 [40], 547.7 [44], and 960 mg/kg [45]. With intraperitoneal route of MG administration, an LD_{50} of 126 mg/kg [46] was reported. Another study using intravenously administered MG and 7OHMG found LD_{50s} of 27.8 and 24.7 mg/kg, respectively [44]. Demise of the animals was preceded by restlessness, tremors, and convulsions.

One study [47] specifically aimed to evaluate the respiratory effects of MG and 7OHMG on male mice. Here, morphine, MG, and 7OHMG were incrementally administered orally. Morphine (3–30 mg/kg) and 7OHMG (3–30 mg/kg) dose dependently depressed mechanical ventilation, while low-dose MG (3 mg/kg) did not produce significant changes in respiration. MG at 10 mg/kg induced significant and prolonged respiratory depression that was not further increased at higher doses (30 and 90 mg/kg). Pretreatment with ketoconazole, a CYP inhibitor, significantly reduced MG-induced respiratory depression, however not 7OHMG; hence, MG was deemed to have a ceiling effect due to metabolic saturation of the CYP3A enzyme.

Three studies did not find an LD_{50}. One administered oral Malaysian alkaloid methanol extract in doses upwards of 1000 mg/kg to male rats without causing deaths [48]. A similar study assessed various Malaysian kratom extracts, including aqueous, and found no deaths at up to 2000 mg/kg [49] when administered to male and female rats. This was also found when MG and 7OHMG were administered to male mice in doses upwards of 30 mg/kg [47].

In one cytotoxicity study [50], MG extract was administered in various concentrations, and cell proliferation was inhibited in a dose-dependent fashion at > 100 µg/mL, with cell death noted at 1000 µg/mL. In a brine shrimp study [51], MG was found to be toxic to at 44 µL/mL, with alkaloid extract and aqueous extracts at 62 and 98 µL/mL, respectively.

Observational Studies and Other Reports

There are 8 studies evaluating data from various sources: five studies review data from the National Poison Data System (NPDS) and two from Poison Control Centers (PCC), with one looking at PCC from outside USA and one contrasting data from NPDS to that from a Thailand PCC. One study extracted data from FDA's Adverse Event Reporting System (FAERS) and one from State Unintentional Drug Overdose Reporting System (SUDORS). Two studies reported on US death certificate data, and UK death registry information, respectively. Two studies evaluated samples available postmortem from toxicology laboratories.

National Poison Data System (NPDS)

NPDS is a national database of information logged by the country's regional poison centers, serving all 50 states, the District of Columbia, and Puerto Rico and is maintained by the American Association of PCC. In addition to uploading to it by the PCCs, NPDS case records are also the result of call reports made by the public and health care providers.

Anwar et al. [52] retrospectively evaluated reports of kratom exposures uploaded to the NPDS between January 2010 and December 2015. A total of 660 calls concerning exposures to kratom were received, with a 10-fold increase noted in 2015 compared to 2010. Cases of polysubstance exposures mostly involved ethanol, other botanicals, benzodiazepines, narcotics, and acetaminophen. Single-kratom exposures were reported in 64.8% of the cases, and individuals were mostly male (71.7%), with a median age of 28 years of age. Medical outcomes associated with kratom exposure were reported as minor (minimal signs or symptoms, which resolved rapidly with no residual disability) for 24.5% of exposures, moderate (non-life threatening, with no residual disability, but requiring some form of treatment) for 41.7%, and major (life-threatening signs or symptoms, with some residual disability) for only 7.4% of exposures. One death was reported in a person who was exposed to kratom in addition to paroxetine and lamotrigine. Details of signs and symptoms were not uniformly available. Where available, these included tachycardia (25.0%), agitation or irritability (23.8%), drowsiness (19.4%), nausea (14.7%), and hypertension (11.7%). A chi-square test showed a significant association between severity of the outcome and multiple versus single exposures.

Eggleston et al. [53] also retrospectively reviewed reports of kratom exposures called into the NPDS between January 1, 2011 and July 31, 2018. A total of 2312 kratom exposures were reported with 935 cases involving kratom as the only substance. Commonly reported symptoms were agitation (18.6%), tachycardia (16.9%), drowsiness (13.6%), and also serious adverse effects such as seizures (6.1%), respiratory depression (2.3%), and cardiac and respiratory arrest (0.6%).

In a more in-depth retrospective review of NPDS reports uploaded specifically by PCCs, Post et al. [54] analyzed exposures to kratom between 2011 and 2017. Unlike Anwar's study, this also covered 2015, a period when public interest in kratom spiked. A total of 1807 kratom exposures were reported during this period, 65% of them occurring during the latter year. Of these, 1174 were kratom-only exposures and 86.9% resulted in one or more clinical effects. Most exposures occurred among male (70.8%), on average 20 years of age (88.9%), and occurred at a residence (86.1%). Among kratom-only exposures, 31.8% resulted in admission to a health care facility, and 51.9% in a serious medical outcome. Multiple-substance exposures were associated with greater odds of admission to a healthcare facility (OR: 2.80; 95% CI: 2.21–3.55) and a serious medical outcome (OR: 2.25; 95% CI: 1.77–2.85) compared with kratom-only exposures. Common clinical symptoms associated with kratom exposures were agitation/irritability (22.9%), tachycardia (21.4%), nausea (14.6%), drowsiness/lethargy (14.3%), vomiting (13.2%), confusion (10.6%), and hypertension (10.1%). Serious clinical effects included seizures (9.6%), respiratory depression (3.6%), coma (3.5%), bradycardia (1.2%), rhabdomyolysis (0.9%), renal failure (0.5%), respiratory arrest (0.4%), and cardiac arrest/asystole (0.4%). Of cases involving only kratom, 51.9% received therapies, most common being IV fluids (52.0%), benzodiazepines (31.3%), oxygen (14.7%), and naloxone (12.5%), and 8.6% of exposures resulted in tracheal intubation. There were eleven deaths associated with kratom exposure, including two that occurred after exposure to kratom only. Substances involved in the deaths included diphenhydramine, ethanol, benzodiazepines, fentanyl, and cocaine.

In a retrospective review of NPDS looking specifically at adults 60 years of age and older, a subgroup accounting for 4.6% of kratom-related calls, Graves et al. [55] found that, between 2014 and 2019, similar neurological (agitation, confusion, tremor, seizures) and cardiovascular (hypertension, tachycardia) hyperadrenergic findings were reported. Calls involving those 70 years of age and older were more likely to involve an adverse reaction (drug interaction) to kratom compared to younger users.

Poison Control

Cumpston et al. [56] performed a retrospective cross-sectional study of electronic PCC data, describing clinical outcomes of kratom exposures between January 1, 2002 and November 30, 2016. A total of twelve cases of kratom-only exposures were identified. Individuals were 25 years of age on average and mostly male. Reported symptoms included tachycardia (42%), agitation (25%), CNS depression (25%), and seizures (25%). Median presenting vital signs included: heart rate of 102 bpm, blood pressure of 151/89 mm Hg, respiratory rate of 20 rpm, pulse oximetry of 99%, and temperature of 37 °C. Electrocardiograms obtained on three patients had a median QRS of 114 ms and QTc of 476 ms, and no dysrhythmias were described. As far as administered therapies, benzodiazepines (33%) were the most frequently used treatment, and 50% of cases were admitted to psychiatry. None of the cases included laboratory confirmation of the presence of MG. One of the twelve cases involved intentional ingestion as a suicide attempt.

Forrester et al. [57] performed a retrospective study to evaluate reports of kratom exposures made to The Texas

Poison Center Network (telephone consultation service that provides information and assists in the management of exposure to substances) between January 1998 and September 2013. No reports involving kratom were identified until 2009. A total of 14 exposures were found involving mostly male ($n = 11$), on average, 20 years of age. Of the 14, twelve ingested kratom, one inhaled, and one inhaled and ingested. Twelve patients were managed at a healthcare facility, and the remaining two were managed at home. Eight of the exposures involved kratom only, and six involved additional substances (wild dagga, wormwood, alprazolam and synthetic cannabinoid, synthetic tryptamine, alcohol, and methamphetamine and risperidone). Four patients had a medical outcome of minor effects, five had moderate effects, one had major effects, two were not followed with no more than minor effect possible, and two were unable to be followed but judged as a potentially toxic exposure. There were no deaths. The reported clinical defects were tachycardia ($n = 5$), hypertension ($n = 4$), agitation ($n = 4$), nausea ($n = 3$), vomiting ($n = 3$), confusion ($n = 3$), tremor ($n = 3$), diaphoresis ($n = 3$), drowsiness ($n = 2$), hallucinations ($n = 2$), mydriasis ($n = 2$), dyspnea ($n = 2$), bradycardia ($n = 1$), abdominal pain ($n = 1$), slurred speech ($n = 1$), hyperventilation ($n = 1$), and elevated creatine phosphokinase ($n = 1$). Of those requiring therapies, administered treatments were intravenous fluids ($n = 6$), benzodiazepines ($n = 4$), other sedation ($n = 2$), antiemetics ($n = 1$), antihypertensive ($n = 1$), and oxygen (n = 1).

A retrospective review study by Trakulsrichai et al. [58] evaluated characteristics of kratom poisoning from exposure cases recorded by the Ramathibodi Poison Center in Thailand. Over a 5-year period, a total of 52 cases were reported, of which 76.9% involved toxicities, and the remainder were withdrawal related. Most common symptoms were heart palpitations (22.5%) and seizures (17.5%), and no deaths were identified.

Davidson et al. [59] contrasted kratom exposure reports between 2010 and 2017 from the Ramathibodi Poison Center (RPC) in Thailand to that from the US NPDS. A total of 160 and 760 cases from the RPC and NPDS, respectively, were identified. The authors found in their analysis that a greater proportion of cases involved co-exposures in Thailand (64.8% versus 37.4%), and that both countries had a similar prevalence of opioid and benzodiazepine co-ingestion. However, the US had more coingestions with other sedatives. Commonly reported effects were tachycardia (30.4%), agitation/irritability (26.2%), and drowsiness (21.1%). Severe medical outcomes were more common in the USA. Four deaths were identified in the USA, one involving single-substance exposure, and two in Thailand, which involved polydrug ingestions.

FDA's Adverse Event Reporting System

Sharma and McCurdy briefly reported on their review of the FAERS database [60]. Between 2011 and 2021, a total of 497 kratom-associated serious cases were found, including 356 deaths. The majority of those cases involved other prescription drugs co-ingested with kratom products [61].

State Unintentional Drug Overdose Reporting System

Olsen et al. [62] published a report outlining the findings from CDC's analysis of data from the SUDORS database. CDC provides funding to 32 states and DC to abstract into SUDORS detailed data on unintentional and undetermined intent opioid overdose deaths from death certificates and medical examiner and coroner reports, including postmortem toxicology results, and kratom is included. Between July 2016 and December 2017, a total of 27,338 deaths by overdose were entered, and of these 152 (0.56%) tested positive for kratom on postmortem toxicology testing, or a medical examiner or coroner-deemed kratom involvement. Kratom was believed to be the cause of death for 91 (59.9%). Of these, only seven tested positive for kratom only, among substances tested for. Postmortem tests detected multiple other substances including fentanyl and analogues, heroin, and benzodiazepines.

Death Certificates

In their study of the NPDS data, Eggleston et al. [53] also briefly reviewed records from a NY state county's medical examiner's office for kratom-associated fatalities. Kratom was listed as the cause of death or contributing factor in the death of four as per county's medical examiner's office.

Gershman et al. [63] submitted a letter to an editorial board, summarizing the findings from a review of Colorado death certificates, which they searched for mentions of kratom or MG between 1999 and 2017. They found a total of 15 certificates where kratom was deemed to have been involved. Of these, 13 were men with a median age of 28 years of age, and eleven involved multi-drug exposures (on average, two to six other drugs, with eight testing positive for opioids). The four attributed to kratom only; all died between 2013 and 2017, and coroners attributed the deaths to MG toxicity. The authors also reviewed autopsy and police reports and performed a comprehensive toxicology screen with high-performance liquid chromatography with tandem mass spectrometry for the three cases, for which residual blood was available. They concluded that 14 of the 15 cases involved multiple drugs (since blood was not available for one of the four kratom-only cases, which succumbed from seizures and cardiorespiratory arrest). The MG levels of the three were 16, 170, and 48 ng/mL.

In the UK, Corkery et al. [64] searched mortality registers for mentions of kratom involvement. A total of 156 deaths were found, mostly males (80%), on average, 32.3 years of age, with substance abuse histories (95%). Of these, only six cases involved MG alone and were accompanied by appropriate testing. The others involved multiple substances with mostly CNS suppressant agents. Death causes noted were toxic effects of kratom and other substances as well as underlying health issues. The autopsy findings were congested/edematous lungs, hypoxic encephalopathy, and anoxic brain injury. In cases where MG was quantified, the blood concentration was 853 (mean) for all cases, 890 for kratom and polysubstance cases, and 398 ng/mL for kratom-only cases.

Laboratory Analyses

One national laboratory undertook a study [65] through which the authors identified postmortem cases from North Carolina, which was screened positive by gas-chromatography-mass spectrometry. They requested samples for directed testing for MG using specific testing parameters. Blood MG concentrations of the 31 cases ranged from 11 to 3300 ng/mL. All cases involved other substances in addition to MG, with opioids (both pharmacological and illicit) detected in 84% of the cases and fentanyl being the most prevalent.

In Sweden, Kronstrand et al. [66] attempted to quantify deaths attributed to krypton, a combination of kratom and *O*- desmethyltramadol. They assessed samples submitted by medico-legal autopsy centers to the country's central laboratory, using a quantitative technique. Over less than 1-year period, a total of nine cases were identified, seven of which were males. On autopsy, all had edema and congestion of lungs present, and blood toxicology contained *O*-desmethyltramadol and MG ranging from 0.02 to 0.18 μg/g for the nine cases.

Discussion

Kratom has a long history of ethnopharmacological use in Southeast Asian countries; however, recent recreational use as part of polydrug combinations and via unregulated products sold in the USA has led to significant adverse effects and involvement in overdose deaths, raising concerns over its safety profile. In 1932, Grewal et al. undertook a study [67] where five volunteers, including the author, consumed in four repeated doses, 50 mg of MG, or 0.65–1.39 g of powdered leaves. No effects other than nausea, vomiting, slight tremors, and an overall cocaine feeling were noted by both groups. Another study explored pharmacokinetics through sub-chronic administration of kratom tea, containing 0.104, 0.166, and 0.192 mg/mL of MG to ten chronic kratom users over 7 days. Resulting MG plasma concentrations were found to display linear pharmacokinetics, ranging from 18–105 ng/mL within ~ 1 h [68]. No adverse effects were reported, aside from mildly elevated blood pressure and heart rate attributed to the stimulant effects of low doses. To date, no other human clinical trial of kratom administration has been conducted.

In this review, we summarized all existing levels of evidence concerning the potential for kratom and its constituents to cause fatal events in efforts to shine light on the risk of overdosing on this botanical. The case reports reviewed here include various anecdotes of toxicities, with the exact paradigms not uniformly defined. Where specified, coingestions of pharmacological and illicit substances with pharmacokinetic and/or synergistic CNS suppressant effects confound the presentations. Overall, toxicities resemble a mix of adrenergic (vasoconstriction, seizures) as well as opioid-like (pulmonary congestion and edema) components. Opioids are involved in presentations in addition to kratom. All except for one of the case reports come from the USA and involve use of various commercial products of undefined purity. The reporting of kratom use in case reports has been criticized as lacking clarity and clinical context [69]. As we found, few describe clear clinical paradigms, MG concentrations are not uniformly reported; the analytical means of detection is not defined, and the time from collection/death to assessment is often unclear. Where MG concentrations are reported, these are not indicative of clear toxicities. Higher concentrations are not always attributed to kratom toxicity, given the confounding coingestion of other drugs. Additionally, in evaluating concentrations from fatalities and near fatalities, MG concentrations span a large concentration range with a significant amount of overlap.

Some of the findings from case reports may be explained by alkaloids' action on postsynaptic alpha-2 adrenergic receptors, which accentuate the effects of sedative, hypnotic, and analgesic agents when coingested. Recent in vitro data also has supported alkaloids' impact on substances that are p-glycoprotein substrates, leading to their clinical toxicity [70]. Alkaloids also impact CYP450 activities when administered with agents using that metabolic pathway, again potentially causing toxicity [71]. They specifically inhibit the 2D6 isoform, an enzyme burdened by a lot of prescribed medications, particularly those that are CNS active [72]. These considerations bear significant importance, particularly in the USA, where consumed products involve concentrated extracts, and alkaloid products with high levels of MG, 7OHMG. Sharma et al. contrasted differences in plasma concentrations of MG between native kratom users in Thailand (Cmax, 0.05–0.26 μM) and autopsy samples in the USA (Cmax upwards of 8.8 μM), which further provide evidence for MG-mediated herb:drug interactions [73, 74].

Of case reports, only one originated from Southeast Asia, where an individual was abusing a kratom concoction made of kratom, cola, and codeine/diphenhydramine cough syrup for psychoactive effects. Worthy of consideration as accounting for the differences in harm between the USA and Asia are the differences in kratom consumption habits, motives for use, and product types available.

Preclinical studies support a dose-related toxicity that resembles more so adrenergic rather than opioid effects, with tremor and seizures preceding death.

Oral administration of total alkaloid extracts to mice and rats found LD_{50s} ranging from 173 mg/kg in Thailand to 591 mg/kg in a Malaysian study. The high content of MG (66% in Thailand versus 12% in Malaysia) in the base crude extract and discrepancy in the chemical constituents of extracts in addition to variations in oral absorption and metabolism between species may explain these differences in lethality. Additionally, the type of a vehicle used to dissolve the extracts also differs across studies. There are two studies that administered Malaysian total alkaloid extracts to rats in doses of 1000 and 2000 mg/kg and found no deaths.

Oral administration of pure MG to mice and rats found LD_{50s} ranging from 200 to as high as 960 mg/kg. One study specifically looked at respiratory effects of alkaloids in mice and found that the 7OHMG dose dependently (3–30 mg/kg) depressed ventilation, while low-dose MG (3 mg/kg) did not; however, this became apparent at higher doses (10 mg/kg) and did not accentuate any further with higher doses. After repeating this with CYP inhibitor pretreatment to prevent conversion of MG to active constituents, the authors concluded that MG has a ceiling respiratory suppressant effect attributed to metabolic saturation of the CYP3A enzyme. The instability of 7OHMG in cellular assays has previously been investigated, as human plasma shows conversion to the more potent metabolites mitragynine pseudoindoxyl [75]. This conversion occurs to a greater extent in humans than other species such as rats and mice, adding to the complexity of making inferences from animal studies.

When Malaysian total alkaloid extract and MG were compared, therapeutic indexes (TI) of 21:1 and 3:1 were determined for MG and alkaloid extract, respectively. The wider TI of MG makes it safer than the alkaloid extract; however, as the authors note, morphine has an even wider TI of 70:1, while cocaine and ethyl alcohol are 15:1 and 10:1, respectively.

Consistently, in all studies, nephrotoxicity and hepatotoxicity developed when high doses were used.

Extrapolations using interspecies allometric scaling for dose conversions to humans are controversial [76]. Assuming the lowest reported oral LD_{50} for MG in rats, the corresponding human equivalent doses (HED) would be 32.4 mg/kg [77]. With the average US female weighing 77.5 kg and the average male weighing 90.6 kg, assuming consumption of high-potency Thailand kratom leaves, one would have to consume 380.5 g or 224 green leaves (female)/444.7 g or 262 green leaves (male) [78]. Low-level consumption in Thailand is known to be approximately 10 leaves (17 g) daily, while high consumption is 30 leaves (50 g).

Interestingly, the extent to which the opioid effects contribute to the toxicity of kratom has not been specifically assessed. There are no lethality studies where naloxone was used to reverse toxic effects.

Observational studies and reports based on registered data provide an overview of the clinical toxicities involving kratom. Here, we see mostly adrenergic effects (agitation/irritability, nausea/vomiting, hypertension, tachycardia, tremors, seizures) with minimal respiratory/opioid-like effects reported. Elderly and clinical populations were found to be more prone to developing adverse effects. Interestingly, one study that contrasted reports from USA and Thailand found that, although polydrug toxicities are more common in Thailand, the USA exposures yield greater clinical severity. This is likely due to the products available in the USA and having more sedative coingestions present, and the reasons for consumption by the US population. US products, particularly extracts, are significantly more potent, which results in greater dose ingestions by the US population [79]. Relying on such data has some limitations, as not all adverse effects associated with kratom are reported to these agencies, and the reported exposures do not necessarily represent an overdose. Given the heterogeneity in entities reporting, clinical information and context are also not present.

Reviews of death certificates show kratom involvement occurs along with other illicits, just like in case reports. It is important to note that MG is not always suspected and, hence, assessed for. MG concentrations ranged from 16–900 ng/mL for polydrug ingestions and 398 ng/mL for kratom-only cases. Autopsy findings revealed congested/edematous lungs, hypoxic encephalopathy, anoxic brain injury; however, majority of cases involved opioid coingestions.

Laboratories expressed the need for standardized collection and analysis of kratom's alkaloids. To date, the testing products and analysis methods have been extremely variable. In assessing autopsy samples involving kratom through a standardized method, blood MG concentrations in the range of 11–3300 ng/mL were found, although all cases involved other substances in addition to MG, with opioids being the most prevalent.

Kratom's safety received support through a comprehensive assessment of the evidence via the 8 factors of the Controlled Substance Act [80]. Here, Henningfield et al. do not disagree that kratom carries a certain mortality risk; however, they report that the anticipated risk is a thousand times lower than the mortality risk associated with opioids [81].

Conclusion

With rising interest in kratom use among the US population, paralleled by increasing warnings of overdose toxicities, it is vital to understand the risks associated with kratom use. Evidence from case reports suggests that use of the kratom products sold in the USA, especially when combined with other sedative illicits and prescribed medications in clinical populations, can have detrimental and lethal consequences due to synergistic drug effects and pharmacokinetic interactions. Animal studies are limited in quality and translatability, and, due to the heterogeneity of methodologies, they yield somewhat inconsistent findings. In all, the alkaloid dose required for demise by seizures and cardiorespiratory failure is high and likely much higher than entailed by traditional human consumption. Observational studies of toxicological data show mostly adrenergic toxicities, with very few opioid-like effects. Reports based on laboratory and autopsy data show fatalities involving kratom almost always involve coingestions of other sedative agents. It is evident that kratom is not a traditional opioid and has both adrenergic and opioid-like toxicities, with the first much more likely to occur in a dose-related fashion than the latter. Taken together, we can conclude that the safety concerns surrounding kratom are mostly related to the quality of the products in the USA, user characteristics and consumption motives, and pharmacokinetic interactions; however, we should be deploying more resources into further studies of alkaloids and well-defined kratom products to determine its exact toxicities.

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Declarations

Conflict of Interest The authors declare no competing interests.

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