

Kratom 101



Agenda

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Key Takeaways + Acknowledgements

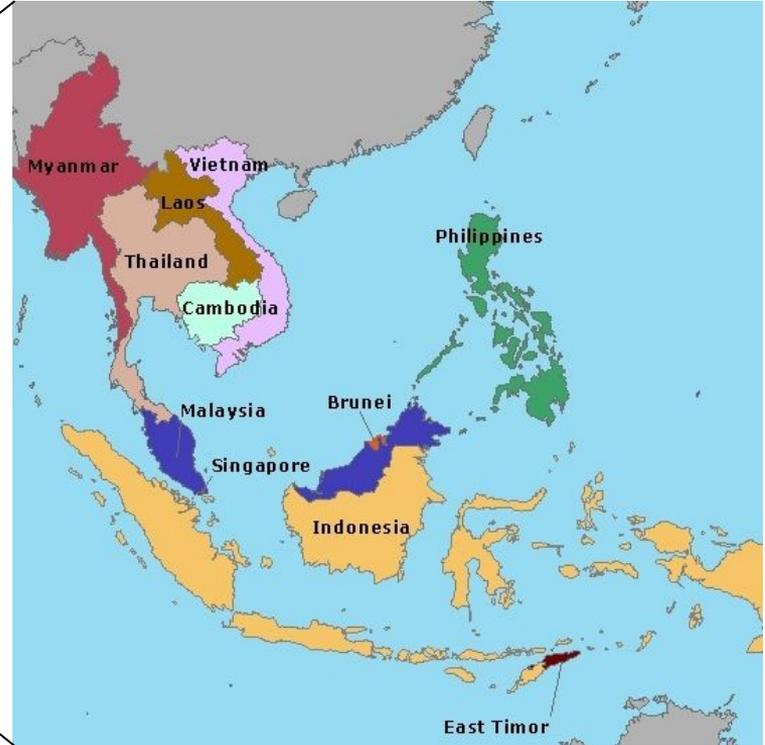
01

History

Kratom: A Plant-based Product



Mitragyna speciosa Korth.



Southeast Asia

Kratom Consumption in Southeast Asia



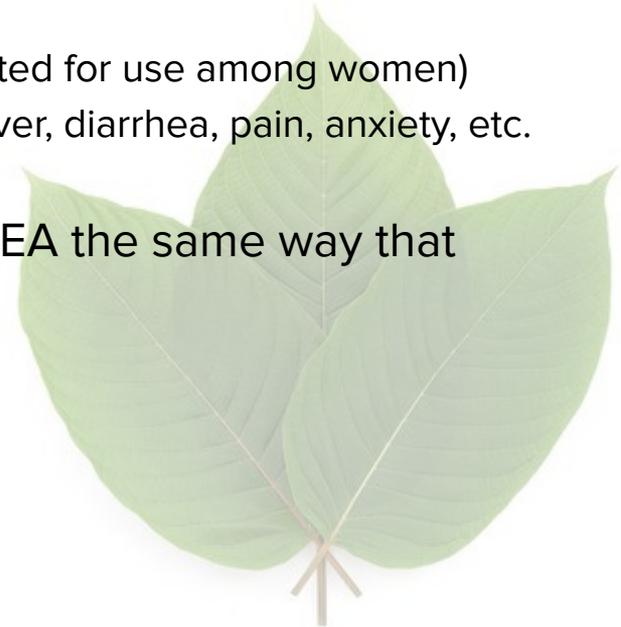
“**decoction**” or tea

chewed leaves

not necessarily viewed as ‘drug use’ -
more like a cup of coffee!

Kratom Use Indigenously / Traditionally in SEA

- Many indigenous uses of the plant
 - Most commonly used by **male laborers** to manage pain and boost energy during the work day
 - Used by men in the evenings in **social settings** (not accepted for use among women)
 - Used as a **household remedy** for various things such as fever, diarrhea, pain, anxiety, etc.
 - Occasionally used in **religious ceremonies**
- Due to these uses, kratom use is **not stigmatized** in SEA the same way that other drugs/alcohol are



Kratom Use Indigenously / Traditionally in SEA

- Kratom use been documented to serve as a **withdrawal mitigation strategy / substitute for opium and/or heroin** in Southeast Asia for almost 200 years
- This history also points to the potential for **kratom dependence, withdrawal, cravings, and addiction**



02

Kratom in the US

Kratom Use in the US

- First reported to come to the US in 1980's or 1990's, but see kratom becoming having more **mainstream use starting in 2010's**
- Estimated number of kratom consumers in the US: **3-15 million**; tend to be:
 - White (non-Hispanic)
 - Male
 - Between 31 and 50 years of age
 - Married or partnered
 - Employed with an annual household income of \$35,000+
 - Have private health insurance
 - Have at least some college education

Kratom is Grown/Processed and Sent to the US



→ Leaves are **harvested and dried** in SEA



→ Leaves are **processed into powders** and sent to the US for distribution

Variety of US Kratom Products/Vendors



Kratom products look **very different** in the US than in Southeast Asia!



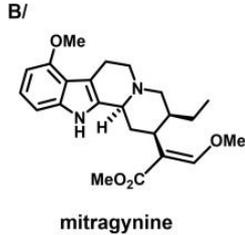
- Most people are buying kratom **online**
- Additionally, people access kratom at **local stores:** head shops / vape stores / gas stations / bodegas / organics stores
- In some states, people can access kratom at specialized **kratom/kava bars**



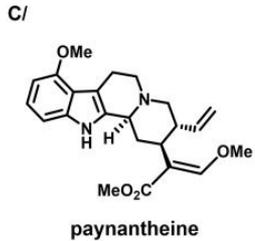
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What Actually is kratom?

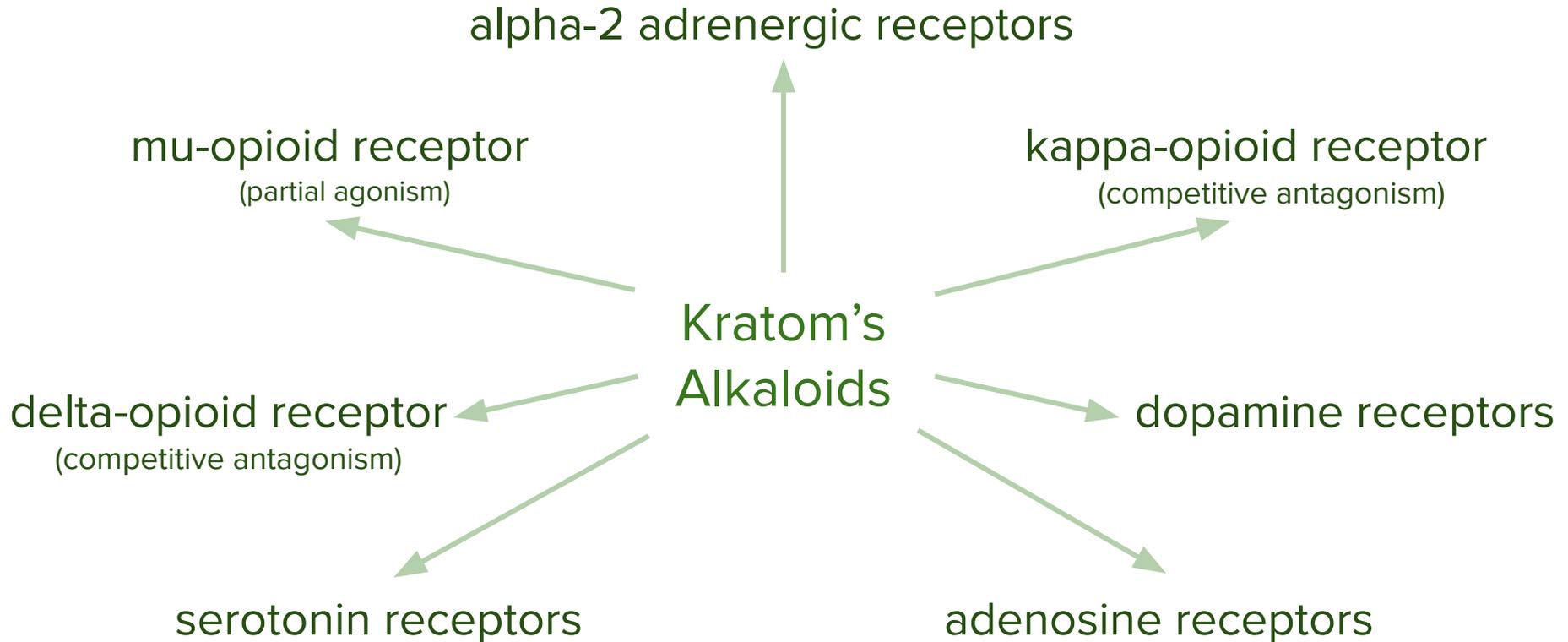
The Key to Kratom's Impact



- The kratom plant has “**alkaloids**,” which are a plant-based class of organic compounds which have **physiological / pharmacological effects** on humans
- Over 40 alkaloids have been isolated from the *Mitragyna speciosa* plant
 - **Mitragynine** is the most researched, primary, active alkaloid that causes the physiological effects seen in humans



Kratom Has Activity at Many Receptor Types



An Herbal Speedball?

- Overall: Kratom is known for having stimulant-like effects at LOW doses and opioid-like effects at HIGH doses
- **Opioid activity** → helps with acute/chronic pain
 - Kratom's alkaloids are often referred to as **“atypical” opioids**
 - Even if they bind to opioid receptors, they DO NOT activate the β -arrestin pathway (this is what is responsible for the respiratory depression seen in other opioids)
 - Studies in rats and case studies show the effects of mitragynine **can be reversed** with naloxone
- **Adrenergic activity** → blocks pain signaling
- **Serotonergic, dopaminergic, adenosine receptor activity** → unclear of the exact pharmacological impacts

04

Harm or Harm Reduction?

Kratom as a Harm?

CASE STUDY:

“In this case of a female in her 40s brought in... appearing hypoxic, obtunded, difficult to arouse, and cyanotic, our differentials included substance use disorder (opioid versus benzodiazepines versus other substances that could cause respiratory suppression), stroke, respiratory failure secondary to infection, cardiogenic causes, and central nervous system infections... **Due to the patient’s responsiveness to naloxone, high on our differential was opioid use disorder with overdose. However, to our surprise, the patient’s urine toxicology was negative for opioid or fentanyl use.** Fortunately, in our case, the patient became alert shortly after interventions and was able to give us a history of **large-volume kratom consumption.**”

Source: Ahmed et al, 2023

Common Kratom Use Side Effects

Constipation

Dizziness

Nausea

Drowsiness

Confusion

Agitation

Vomiting

Rare Adverse Outcomes / Toxicity

(if used in high doses, concentrated products, etc.)

Seizures

Coma

Respiratory Depression

Cardiac Arrest

Rhabdomyolysis

Renal Failure

Bradycardia

Respiratory Arrest

Kratom-Drug Interactions

Overdose

Death

Common Kratom Withdrawal Symptoms

- Muscle spasms
- Diarrhea
- Lack of appetite
- Fever
- Pain
- Runny eyes/nose
- Mood swings
- Restlessness/disturbed sleep
- Sadness

*Among those who use opioids and kratom, these kratom withdrawal symptoms are reported to **not be as strong/severe** as opioid withdrawal.*

+ Potential for Cravings / Dependence

2012: DEA Lists Kratom as a “Drug of Concern”

XI. Drugs of Concern

Kratom

WHAT IS KRATOM?

Kratom is a tropical tree native to Southeast Asia. Consumption of its leaves produces both stimulant effects

prohibitions against the possession and use of kratom. The FDA has not approved Kratom for any medical use. In addition, DEA has listed kratom as a Drug and Chemical of Concern.

2016: MMWR on Poison Center Calls

Morbidity and Mortality Weekly Report

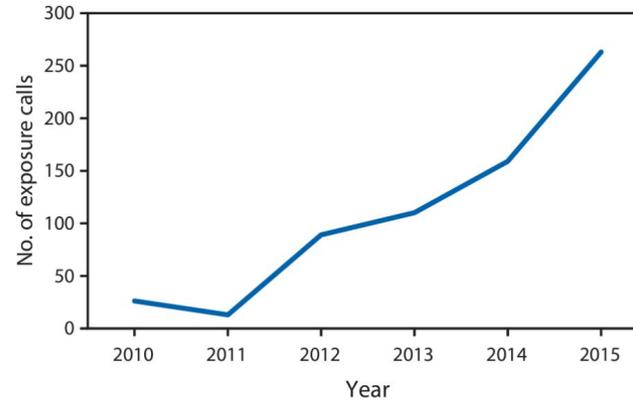
Notes from the Field

Kratom (*Mitragyna speciosa*) Exposures Reported to Poison Centers — United States, 2010–2015

Mehruza Anwar, MD¹; Royal Law, PhD¹; Josh Schier, MD¹

Kratom (*Mitragyna speciosa*) is a plant consumed throughout the world for its stimulant effects and as an opioid substitute (1). It is typically brewed into a tea, chewed, smoked, or ingested in capsules (2). It is also known as Thang, Kakuam, Thom, Ketum, and Biak (3). The Drug Enforcement Administration includes kratom on its Drugs of Concern list (substances that are not currently regulated by the Controlled Substances Act, but that pose risks to persons who abuse them), and the National Institute of Drug Abuse has identified kratom as an emerging drug of abuse (3,4). Published case reports have associated kratom exposure with psychosis, seizures, and deaths (5,6). Because deaths have been attributed to kratom in the United States (7), some jurisdictions have passed or are

FIGURE. Number of reported exposure calls to poison centers related to kratom use, by year — National Poison Data System, United States and Puerto Rico, January 2010–December 2015



2016: DEA Tries to Schedule Kratom

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-442]

**Schedules of Controlled Substances:
Temporary Placement of Mitragynine
and 7-Hydroxymitragynine Into
Schedule I**

AGENCY: Drug Enforcement
Administration, Department of Justice.

ACTION: Notice of intent.

SUMMARY: The Administrator of the Drug Enforcement Administration is issuing this notice of intent to temporarily schedule the opioids mitragynine and 7-hydroxymitragynine, which are the main active constituents of the plant kratom, into schedule I pursuant to the temporary scheduling provisions of the Controlled Substances Act. This action

August: Notice of Intent



October: Withdrawal Notice



DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-442W]

**Withdrawal of Notice of Intent to
Temporarily Place Mitragynine and 7-
Hydroxymitragynine Into Schedule I**

AGENCY: Drug Enforcement
Administration, Department of Justice.

ACTION: Withdrawal of Notice of Intent;
Solicitation of Comments.

SUMMARY: On August 31, 2016, the Drug Enforcement Administration (DEA) published in the **Federal Register** a notice of intent to temporarily place mitragynine and 7-hydroxymitragynine, which are the main psychoactive constituents of the plant *Mitragyna speciosa*, also referred to as kratom, into schedule I pursuant to the temporary

2017: FDA Issues a Public Health Advisory

*“FDA will continue to warn the public against the use of kratom for medical treatment... **Therefore, kratom is not lawfully marketed in the U.S. as a drug product, a dietary supplement, or a food additive in conventional food.**”*

2018: FDA Issues Warning Letters to Vendors

FDA NEWS RELEASE

FDA warns companies selling illegal, unapproved kratom products marketed for opioid cessation, pain treatment and other medical uses

*“As we work to combat the opioid epidemic, we cannot allow unscrupulous vendors to **take advantage of consumers by selling products with unsubstantiated claims that they can treat opioid addiction.**” - FDA Commissioner Scott Gottlieb, M.D*

Current Kratom Legal Landscape



Blank: States where kratom is unregulated

Red: States where kratom is banned

Green: States that have passed the Kratom Consumer Protection Act (KCPA)

Currently: Kratom Increasingly in the News



*Similar to other drugs, see **drug hysteria** playing a role in media...*

Source: Tampa Bay Times, 2023

What About Kratom as Harm Reduction?

REDDIT CASE STUDIES:

- (1) “Essentially, compared with my relationship to alcohol and compared with others’ drug habits, kratom **is a miracle**. My life has become infinitely better - my job, marriage, really all of my relationships, fitness, general happiness! I use kratom once a day and sometimes take days off to get better effects. **It saved my life.**”
- (2) “So now I’ve totally **stopped using traditional opiates and opioids** (I still take kratom, and plan to use kratom so long as availability persists). It easily changed my life.”
- (3) “I took kratom for several weeks and that really sustained me, likely **couldn’t have quit [hydrocodone] without it.**”

Source: Smith et al, 2021

Reported Benefits from Use

Increase Focus

Elevate Mood

Manage Depression

Manage PTSD

Reduce Use of Opioids

Relieve Chronic Pain

Relieve Acute Pain

Manage Anxiety

Increase Energy

Manage Withdrawal Symptoms

+ **Kratom as a Tool if Limited MOUD Access?**

KEY → *Hard to evaluate specifics... there have been no rigorous clinical trials published to date (largely due to product inconsistencies)... information based on self-report / case studies*

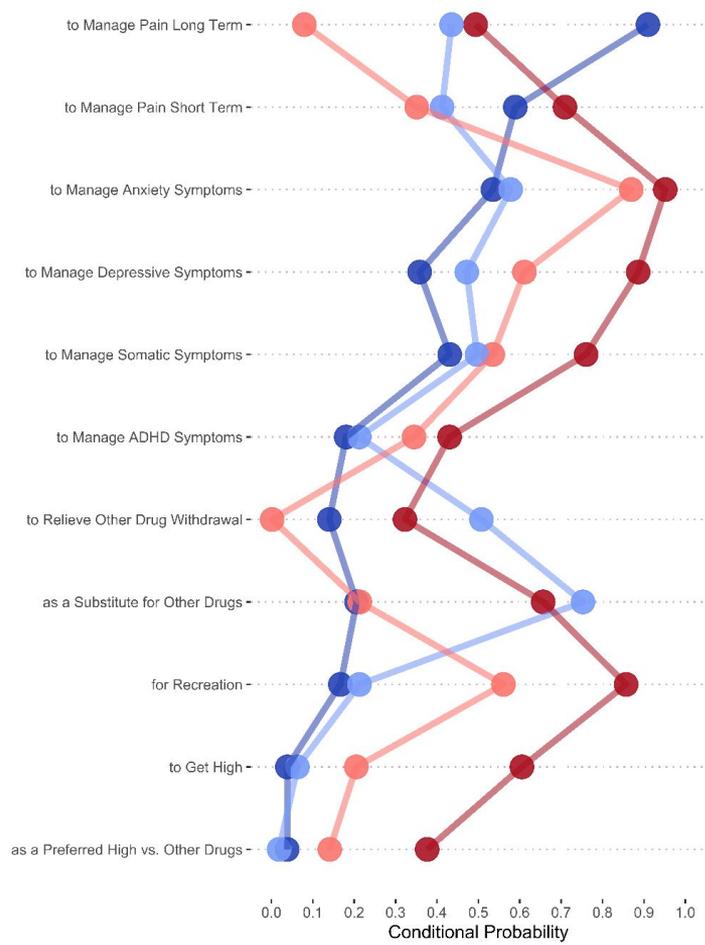
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Emerging Kratom Research

Motivations or Reasons for Kratom Use

LCA Conditional Item Probabilities by Class Assignment

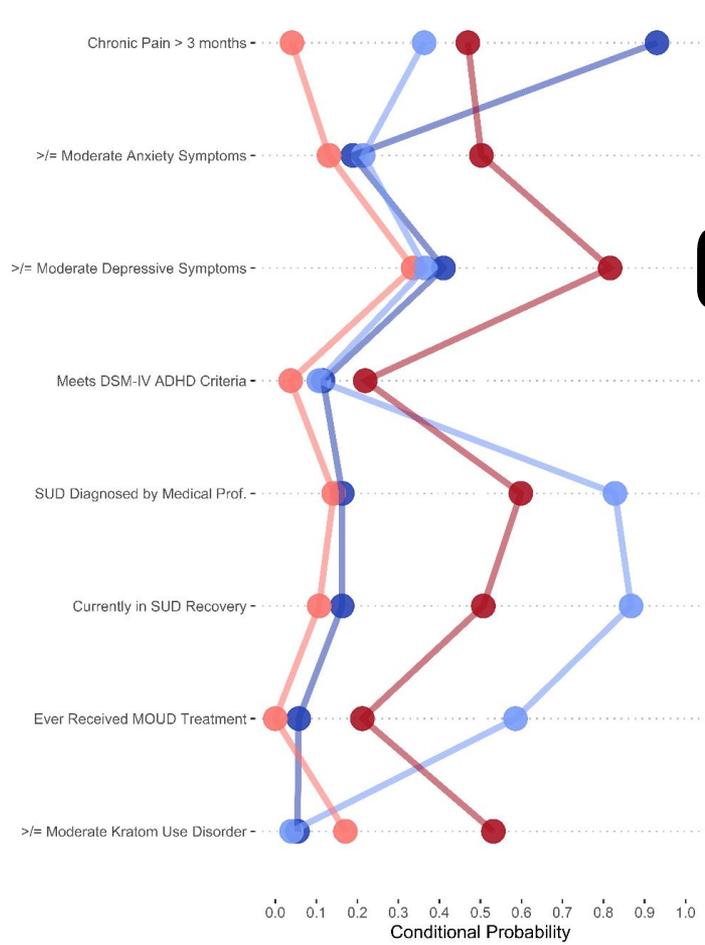
Class ● Class-1 (32%) ● Class-2 (19%) ● Class-3 (25%) ● Class-4 (24%)



Survey Measures Corresponding to Motivation Endorsements

LCA Conditional Item Probabilities by Class Assignment

Class ● Class-1 (32%) ● Class-2 (19%) ● Class-3 (25%) ● Class-4 (24%)



4 Classes of Kratom Consumers in the US

- Pain Txt
- SUD Txt
- Low Anx/Dep
- High Anx/Dep

Sources: Hill et al, 2024

Kratom Use → DSM-5 Substance Use Disorder?

	DSM-IV Abuse ^a		DSM-IV Dependence ^b		DSM-5 Substance Use Disorders ^c	
Hazardous use	X	} ≥1 criterion	-	} ≥3 criteria	X	} ≥2 criteria
Social/interpersonal problems related to use	X		-		X	
Neglected major roles to use	X		-		X	
Legal problems	X		-		X	
Withdrawal ^d	-		X		X	
Tolerance	-		X		X	
Used larger amounts/longer	-		X		X	
Repeated attempts to quit/control use	-		X		X	
Much time spent using	-		X		X	
Physical/psychological problems related to use	-		X		X	
Activities given up to use	-		X		X	
Craving	-		-		X	

Findings on Kratom Use Disorder

TABLE 2. KUD Symptoms Reported by Survey Participants, Stratified by Qualifying for a Potential KUD

Sample Characteristics	Full Sample (N = 2061)		KUD (n = 525)		No KUD (n = 1536)		P*
	Frequency	%	Frequency	%	Frequency	%	
Kratom use disorder symptoms							
Tolerance	648	31.4	427	81.3	221	14.4	<0.0001
Withdrawal	447	21.7	357	68.0	90	5.9	<0.0001
Cravings	340	16.5	298	56.8	42	2.7	<0.0001
Increased use	305	14.8	281	53.5	24	1.6	<0.0001
Inability to cut down use	183	8.9	179	34.1	4	0.3	<0.0001
Continue to use despite physical/psychological problems	106	5.1	104	19.8	2	0.1	<0.0001
Continue to use despite social or interpersonal problems	83	4.0	75	14.3	8	0.5	<0.0001
Spending time to obtain, use, or recover	58	2.8	55	10.5	3	0.2	<0.0001
Impacts work or social life	49	2.4	49	9.3	0	0	<0.0001
Using in physically hazardous situations	44	2.1	42	8.0	2	0.1	<0.0001
Failing to fulfill work, home, or school obligations	34	1.7	33	6.3	1	0.1	<0.0001
Severity							
Mild	—	—	347	66.1	—	—	
Moderate	—	—	105	20.0	—	—	
Severe	—	—	73	13.9	—	—	

* P value is for chi-square test, comparing KUD with no KUD.

KUD indicates kratom use disorder.

Findings on Kratom Use Disorder

Table 4

The top half of the table displays odds ratios (OR), pseudo-R2, and Cohen's d estimates from multivariable logistic models examining participant reports of kratom use disorder symptom experiences. The bottom half of table displays results from a zero-inflated negative binomial model of kratom use disorder (KUD) symptom counts and "excess" zeros. Count model interval rate ratio (IRR) is the rate of increasing KUD symptom counts per unit of the explanatory variable, and zero-inflated model ORs provide the change in likelihood of being an "excess" zero per unit of the explanatory variable.

Self-reported Kratom Use Disorder Symptoms	Standardized Dose Amount (z-score)	Dose Frequency (Kratom Doses/Day)	Female sex	Pseudo R2	Cohen d
	OR [95% CI]	OR [95% CI]	OR [95% CI]		
Used More Than Intended	1.04 [0.87, 1.23]	1.21 ^{***} [1.10, 1.34]	0.78 [0.54, 1.13]	0.12	0.74
Unsuccessful Quit/Reduce Attempts	1.03 [0.85, 1.26]	1.25 ^{***} [1.12, 1.39]	0.66 [0.44, 1.01]	0.08	0.59
Spend a Lot of Time Using/Acquiring	1.20 [0.89, 1.61]	1.39 ^{***} [1.19, 1.63]	0.51 [0.25, 1.06]	0.13	0.77
Cravings Or Urges	1.21 [*] [1.03, 1.43]	1.20 ^{***} [1.09, 1.33]	0.59 ^{**} [0.41, 0.84]	0.10	0.67
Major Role Interference	1.70 ^{**} [1.16, 2.50]	1.70 ^{***} [1.34, 2.15]	0.75 [0.23, 2.44]	0.29	1.28
Use Despite Social Problems	0.89 [0.60, 1.31]	1.26 [*] [1.05, 1.51]	0.37 [*] [0.14, 0.93]	0.13	0.77
Gave Up Important Activity	1.01 [0.62, 1.64]	1.72 ^{***} [1.35, 2.18]	0.42 [0.11, 1.59]	0.28	1.25
Physically Hazardous ^a	-	-	-	-	-
Use Despite Medical Problem	1.08 [0.81, 1.42]	1.41 ^{***} [1.22, 1.62]	0.78 [0.42, 1.47]	0.14	0.81
Tolerance	1.14 [0.97, 1.35]	1.16 ^{**} [1.05, 1.28]	0.88 [0.63, 1.24]	0.07	0.55
Withdrawal	1.25 ^{**} [1.06, 1.47]	1.27 ^{***} [1.15, 1.41]	0.65 [*] [0.46, 0.91]	0.13	0.77

Kratom Vendor Research

inconsistency!

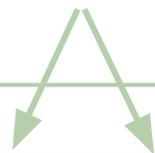


Table 1 Characteristics of eligible AKA GMP qualified vendors

Company Name	URL	Kratom Products	Other Products	Disclaimer	Age for Entry
1836 Kratom	https://www.1836kratom.com/	Powdered tea leaf, capsules, liquid extracts	None	Yes	No
Austin Organic Village	https://austinorganicvillage.online/	Powder, capsules, extracts, blends, leaves	None	Yes	Yes, 21 +
Authentic Kratom	https://www.authentickratom.com/	Crushed leaf, powder, extract, capsules	Face mask, Incense	Yes	Yes, 18 +
Buy Kratom Bulk USA	https://buykratombulkusa.com/	Powder, capsules	None	Yes	No
Chief Kratom	https://chiefkratom.com/	Extracts	None	Yes	No
Choice Botanicals	https://choicekratom.com/	Powder, capsules, extracts	THC, rolling paper	No	Yes, 18 +
Christopher's Organic Botanicals	https://christophersorganicbotanicals.com/	Tea powder, tea, capsules, crushed leaf, extracts	None	Yes	No
Crisp Kratom	https://crispkratom.com/	Gummies, capsules, powder	None	Yes	Yes, 18 +
First Coast Tea	https://www.firstcoasteaco.com/	Tea	Essential oils, kava, herbal soaps, coffee, teas, botanicals, apparel, posters, edible film pouches	No	No
Golden Rule Botanicals	https://goldenrulebotanicals.com/	Tea, blends	CBD, shilajit, kava, subscription boxes, teas, apparel, cups, edible film pouches	Yes	No

Kratom In the Context of Polyuse

- Kratom is often used by people who also use other substances
 - Most kratom-related overdose deaths have another substance involved (e.g., fentanyl, opioids, benzodiazepines, etc.)

Table 1

Sociodemographic information and substances identified in the coroner's report for each case.

Case #	Age range	Race	Sex	Mitragynine (Kratom)	Fentanyl	Other opioid	Benzodiazepine	Cannabis	Antihistamine	Antidepressant	Antipsychotic	Antiepileptic
1	35–40	White	Female	+	–	–	+	–	+	+	+	+
2	45–50	White	Male	+	+	+	–	–	+	–	–	–
3	25–30	White	Male	+	+	–	–	+	–	–	–	–
4	45–50	White	Male	+	+	–	–	–	+	–	–	–

In all cases race was reported as white, the mode of death was accidental, cause of death was toxicity. Five-year age ranges used in place of exact age to comply with *Frontiers in Psychiatry* guidelines for decedent health information.

Synthetics and Semi-Synthetics

Southeast Asia



Mitragyna speciosa



fresh kratom leaves
for chewing



tea-like decoction of
kratom leaves

United States



dried kratom leaves
in powder-form



extracts / concentrates
of whole leaf product



whole leaf powder
in teas and capsules



extracts / concentrates
of Mitragynine



7-hydroxymitragynine
products

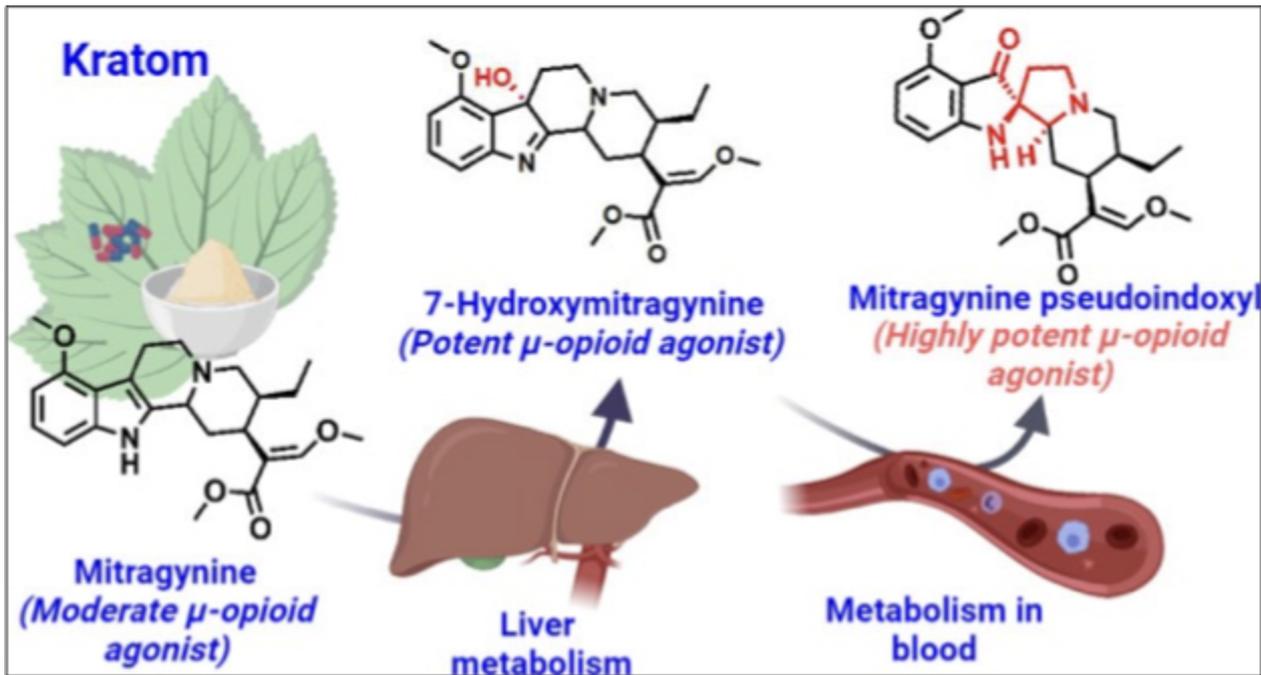


Mitragynine pseudo-
indoxyl products

Time







Synthetics and Semi-Synthetics

- **7-hydroxymitragynine (7-OH)** is the oxidized *derivative* of mitragynine
 - This is of growing interest due to providing analgesic effects via the mu-opioid receptor
 - 7-OH has 10-22 greater binding affinity at the mu-opioid receptor than morphine
- We are also interested in **mitragynine pseudoindoxyl**
 - This ALSO is of growing interest due to providing analgesic effects via the mu-opioid receptor
 - Pseudo is nearly as potent as fentanyl!
- The safety of these molecules in humans have **NOT been studied.**
- These products are often **mislabeled as “kratom”** when sold.
- There are very few regulations on the sale of 7-OH or pseudo products in the US

06

Key Takeaways + Acknowledgements

Key Takeaways

- Kratom is a **complicated** plant that does numerous things to the brain/body
- Indigenous use in Southeast Asia looks **very different** from use in the US
- **Kratom use disorder** is prevalent, though largely mild
 - Some researchers/physicians support use of buprenorphine for treating KUD
- There is still **much we do not know** about kratom and its impacts!
- There are a growing number of **7-OH and pseudo** products on the online market
 - These are highly potent products → emerging public health concern that needs more research

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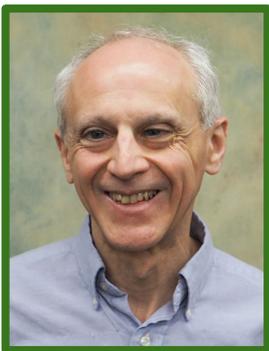
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Real-world Assessment, Prediction, and
Treatment Unit at NIDA

A white ceramic bowl filled with a fine, light green powder is the central focus. The bowl sits on a rustic wooden surface, surrounded by several large, vibrant green leaves with prominent veins. The text "Thank you!!!" is overlaid in a bold, dark green font on the left side of the bowl.

Thank you!!!

Questions?