UF College of Pharmacy
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The addiction and harm reduction potential of kratom in substance use disorders

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https://www.healthlogus.com/health-benefits-of-kratom-leaves/

Disclosure notice

Oliver Grundmann has served as an expert witness in civil and criminal cases related to kratom and other drugs that can cause impairment.

He has nothing else to declare.

Objectives

At the end of the presentation, learners will be able to:

1. Translate the complex pharmacology of kratom into clinical presentation, uses of kratom, and adverse effects.
2. Identify the signs and symptoms associated with “kratom use disorder”.
3. Apply the scientific and clinical knowledge about kratom to inform your counseling of patients and other healthcare professionals.
4. Characterize the limitations of kratom use in regard to dose, frequency, and particular kratom products.

Outline

1. Introduction to the botany and chemistry of kratom
2. Traditional uses of kratom in Southeast Asia and use patterns
3. Pharmacology of kratom alkaloids with emphasis on opioid, adrenergic, and serotonergic receptors
4. Real world data about kratom use based on surveys and observational studies
5. Potential drug interactions & toxicity
6. Best clinical practices in counseling and advising kratom users with an emphasis on kratom products

What is Kratom

- Kratom is a tree (*Mitragyna speciosa* Korth., Rubiaceae) native to south-east Asia, sub-tropical and tropical regions
- Kratom is also a drug:
  - Fresh leaves that are chewed for both stimulant and analgesic effects
  - Dried leaves used to prepare tea
  - Powdered preparations in the West
  - Primarily exported from Indonesia to US
- Leaves contain active ingredients
  - Indole alkaloids **mitragynine** and **7-hydroxymitragynine**, among others

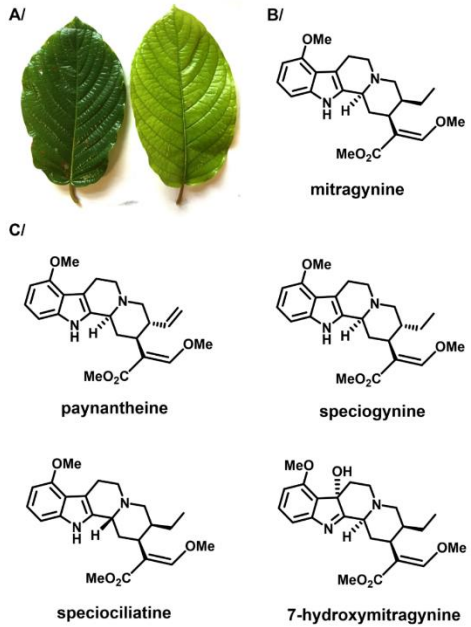
Source(s): Int J Legal Med. 2016 Jan;130(1):127-38

Kratom in Southeast Asia

Source(s): Current Opinion in Psychiatry33(4):312-318, July 2020.

Mitragyna alkaloids

- Mitragynine is most abundant alkaloid
  - Acts as partial agonist at μ-opioid receptors with low potency compared to morphine
  - Acts as competitive antagonist at κ-opioid receptor and shows negligible affinity for δ-opioid receptor
- 7-hydroxymitragynine presents with high potency
  - Acts as partial agonist at μ-opioid receptors with higher affinity than morphine
  - Acts as competitive antagonist at both κ-opioid and δ-opioid receptors with weaker affinity
  - Not present in native, fresh kratom leaf



Source(s): Neuropharmacology. 2018 May 15;134(Pt A):108-120

The dose and the effect

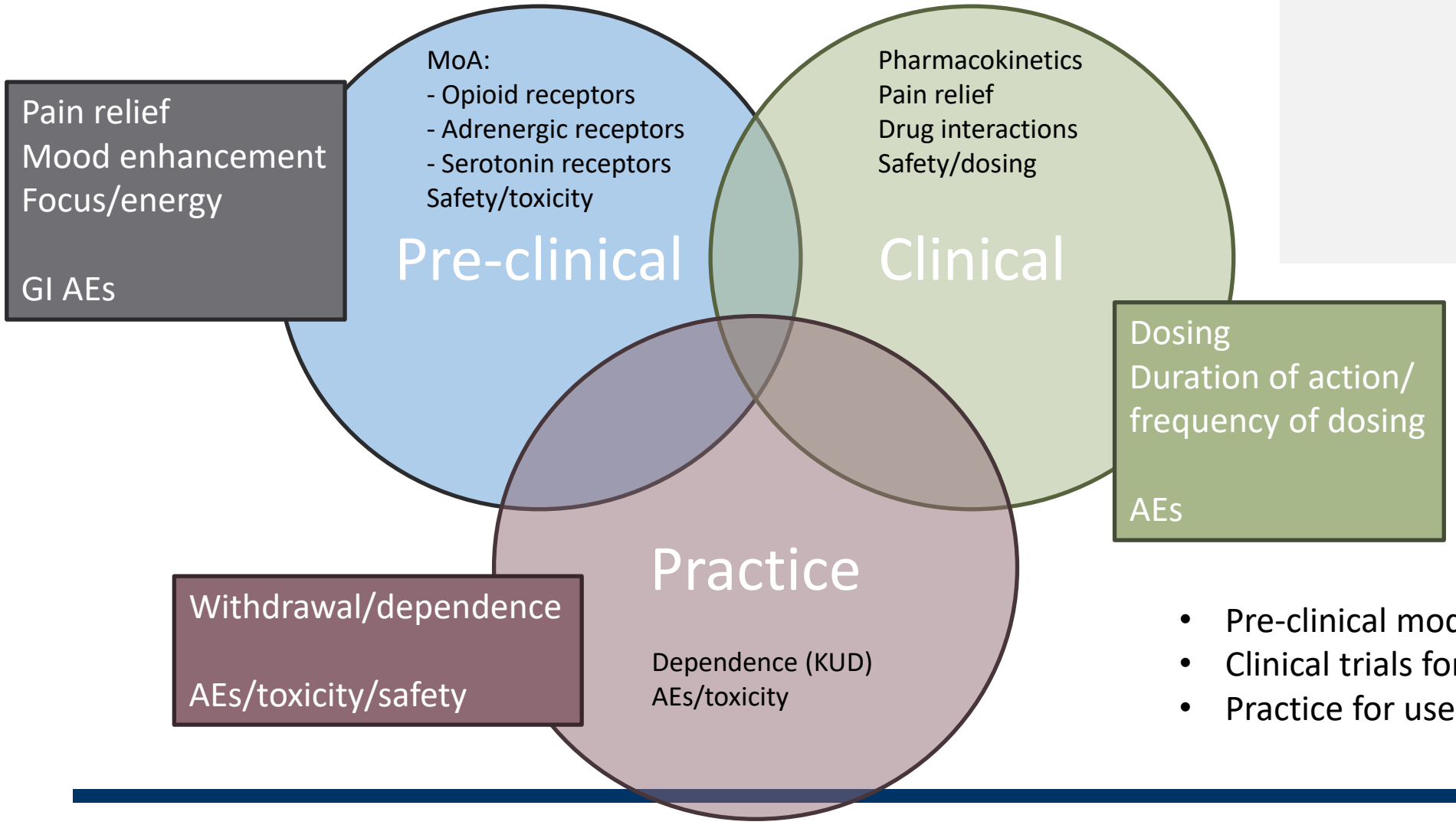
- Oral doses of Kratom exert distinct effects
  - Doses ranging from 1-5 g mainly cause mild stimulant effects, but may also cause muscle relaxation
  - Doses from 5g up to 15g are usually taken for analgesic effects and may also cause constipation, tachycardia, hypotension, dizziness, etc.
  - No indication of other routes of administration (although smoking has been occasionally reported)
- Kratom-only fatalities are rare, majority are polydrug exposures

Table 1 Pharmacological effects of kratom

	Low dose (1–5 g)	High dose (5–15 g)
Stimulant effects	Increased alertness Physical energy Talkativeness Sociable behavior	Tachycardia
Sedative/opioid-like effects	Loss of muscle coordination	Constipation Dizziness Hypotension
Adverse effects	Itching Nausea Loss of appetite Increased urination	Dry mouth Sweating

Source(s): Int J Legal Med. 2016 Jan;130(1):127-38

Connecting the … dots



- Pre-clinical models for MoA, DI, safety
- Clinical trials for indications & safety
- Practice for use & epidemiology

Kratom in the US

Source(s): Current Opinion in Psychiatry33(4):312-318, July 2020.
https://www.tampabay.com/investigations/2023/12/09/tampa-bay-times-tested-20-kratom-products-heres-what-we-found/

Kratom in the US

- Kratom formulations
  - Kratom powder
    - Native, unaltered dried kratom leaf powder
      - Does contain alkaloids in amounts like the fresh leaf material
      - Most clinical data is based on native kratom leaf material
    - Extracted kratom powder
      - Can contain higher amounts of alkaloids, usually “full spectrum” i.e., containing alkaloids in the same ratio as the native kratom leaf powder
    - Concentrates & isolates
      - Isolated single alkaloids (e.g., mitragynine, 7-hydroxymitragynine, or mitragynine pseudoindoxyl) or concentrated alkaloids, effects may differ from native leaf material
  - Other formulations
    - Tablets, capsules: circumvent unpleasant taste to enhance palatability or increase dose tolerance
    - Liquids, elixirs, tinctures: can be flavored, contain other substances or supplements
    - Edibles, chewables: often flavored for palatability, can contain concentrates or isolates

Kratom in the US

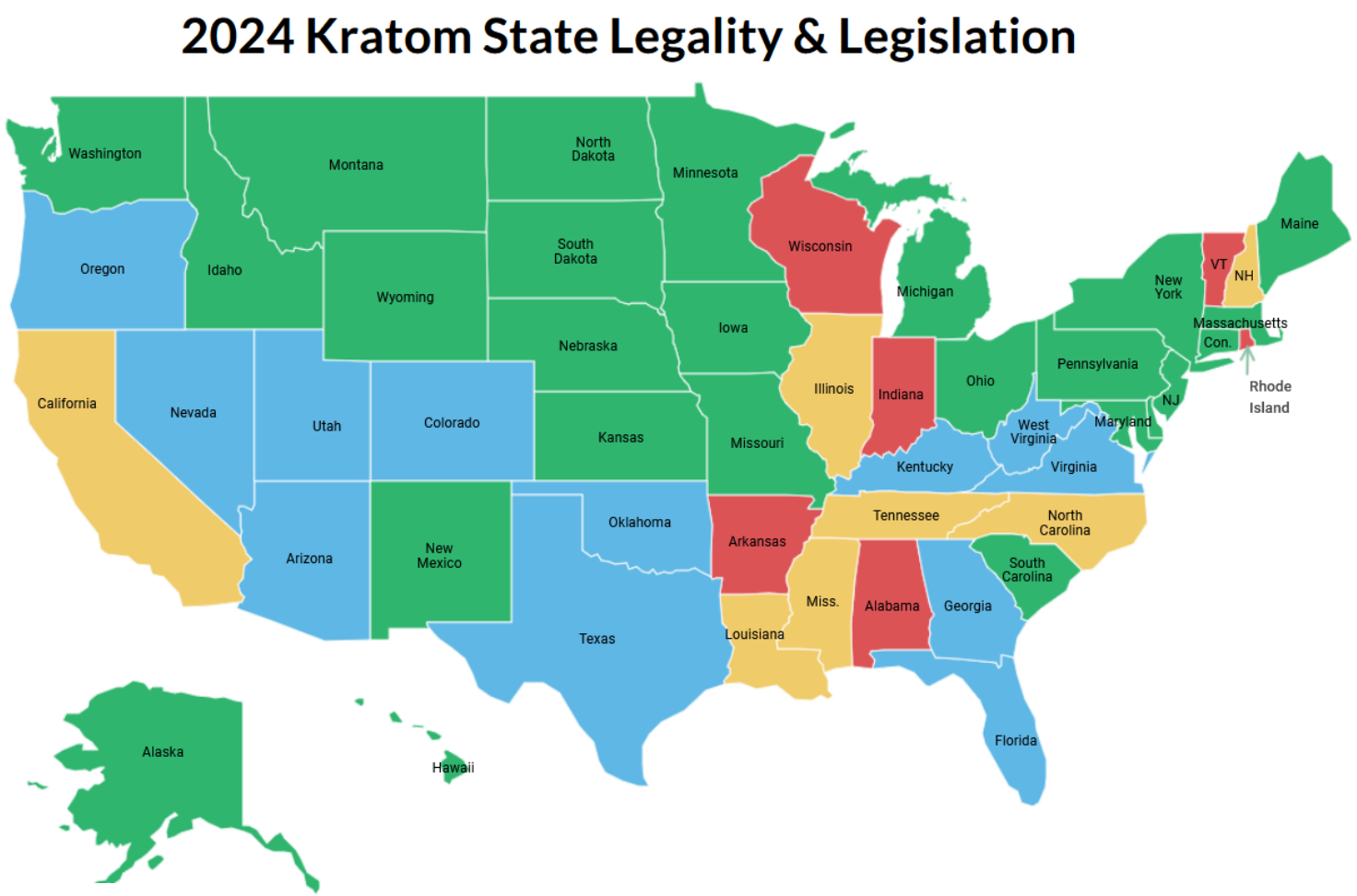
- Kratom formulations
  - Contaminations not uncommon
    - Primarily heavy metals (lead and nickel)
    - Bacteria and fungi (most natural because of leaf material) with one outbreak of Salmonella reported
  - Adulteration
    - Kratom products have been adulterated with opioids
    - 7-hydroxymitragynine was detected in high amounts in several products a few years ago

Source(s): Int J Environ Res Public Health. 2020 Jul 30;17(15):5512.
J Emerg Med. 2022 Jul;63(1):e28-e30.
J Med Toxicol. 2016 Dec;12(4):341-349.

Kratom in the US

- Regulations
  - No federal oversight, not classified as a dietary supplement but new dietary ingredient
    - Not approved as new dietary ingredient by FDA
  - FDA issued import alert for kratom products, classifying them as adulterants
  - Several states have adapted regulations such as the Kratom Consumer Protection Act
    - Requirements on labeling and quality standards, how to sell and to whom
    - Some have adverse effects and warnings stated

Kratom in the US



Legal kratom states that have passed the KCPA are in Blue

Legal kratom states are in Green

States with some known local bans are in yellow

States with kratom bans are in Red

States with proposed bans are purple

Source(s): https://www.americankratom.org/aka-in-your-state

Prevalence of Kratom use

- Current estimates vary widely
  - 0.7% past-year kratom use was associated with higher odds of opioid use disorder (Palamar, *Am J Prev Med*, 2021)
  - 1.3% lifetime prevalence of kratom use from 2019 NSDUH with 18-fold increase among opioid use disorder patients (Xu et al., *Prim Care Companion CNS Disord*, 2021)
  - 6.1% lifetime prevalence for kratom use in survey with up to 48% reporting diagnosed addiction (Covvey et al., *J Addict Dis*, 2020)
  - 0.8% past-year and 1.3% lifetime prevalence of kratom use from NMURx program survey, higher use of illicit and prescription drugs for non-medical reasons (Schimmel et al., *Addiction*, 2021)
- Caveat: Cause and Effect of Kratom use regarding substance use has not been determined (“chicken and egg dilemma”)

The common Kratom user

- Kratom user surveys repeatedly confirmed demographics of average user:
  - Middle-aged user, approximately 60/40 male/female
  - Mostly Caucasian (85-95%)
  - Most married or partnered (55-65%)
  - Middle-class income ($35K-$60K)
  - Employed with health insurance (55-70%)
  - Majority Higher Education (AA, BS, or advanced degree)
- Estimated number of active kratom users based on imported kratom ranges from 2-20 million in the US (Henningfield et al., *Prev Med*, 2019)

The common Kratom user

Table 3. Prior or concomitant use of other substances with kratom.

	Frequency	Percent
Have you taken/Are you taking Kratom in combination with other drugs/ substances?		
Yes	1308	25.7
No	3792	74.3
If you have received treatment, when did you last use the drug(s) of choice?		
Still taking	50	5.2
Less than 6 months	111	11.6
1–2 years	179	18.6
2–5 years	282	29.3
More than 5 years	339	35.3
Which drug(s) have you used/are you using which led you to seek treatment (select all that apply)? Due to multiple selection of drugs, percentages do not add up to 100%.		
Fentanyl or other synthetic opioids	410	18.53
Methadone or other prescribed medications to treat opioid/heroin dependence	370	16.72
Benzodiazepines	299	13.51
Heroin	238	10.75
Others	209	9.44
Cocaine	161	7.28
Cannabis (marijuana, hashish)	150	6.78
Amphetamine	137	6.19
CBD (Cannabidiol) oil	100	4.52
Hallucinogenic mushrooms	33	1.49
Kava	31	1.40
Ketamine or other anesthetic/dissociative drugs	24	1.08
Synthetic cannabinoids	18	0.81
Mephedrone or any other synthetic cathinones	15	0.68
Tryptamines	11	0.50
Phenylethylamines (e.g. 2C-E, AL-LAD, 4-HO-MiPT)	7	0.32

- Majority (94.8%) of kratom users discontinue use of other recreational drugs within 6 months of starting kratom use (Grundmann et al., *Am J Drug Alc Abuse*, 2022)

Self-reported uses of Kratom

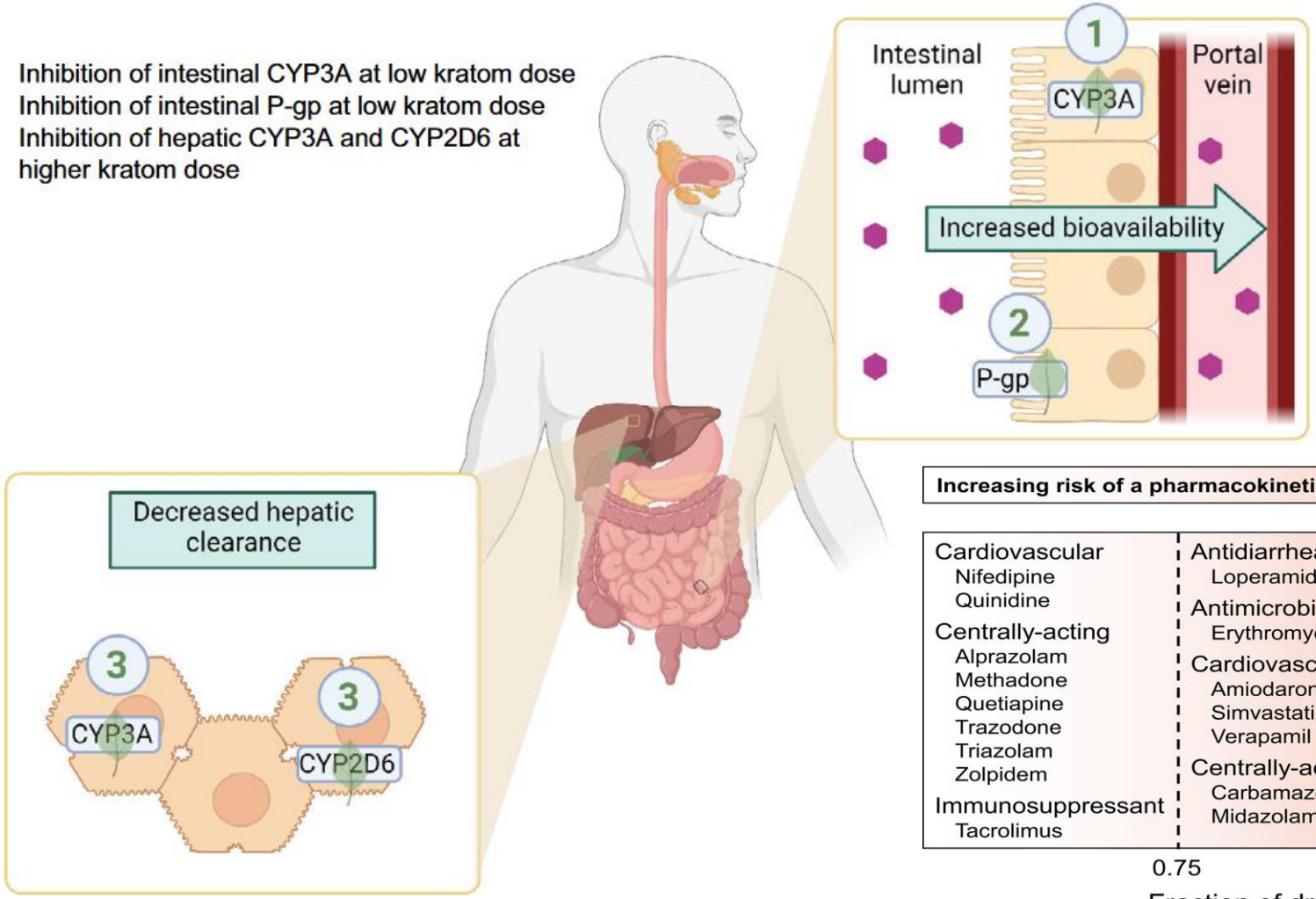
- Kratom user surveys repeatedly indicate several self-treatment indications for kratom use:
  - 70-90%: Psychiatric conditions are most common (depression, anxiety, PTSD, ADHD)
  - 65-85%: Acute and chronic pain (arthritic conditions, fibromyalgia, back pain)
  - 30-45%: Mitigation of prescription medicine withdrawal symptoms
  - 7-25%: Mitigation of illicit drug withdrawal symptoms
- Most kratom users have chronic health conditions and add kratom on top of existing medication regimens: potential for DDIs!

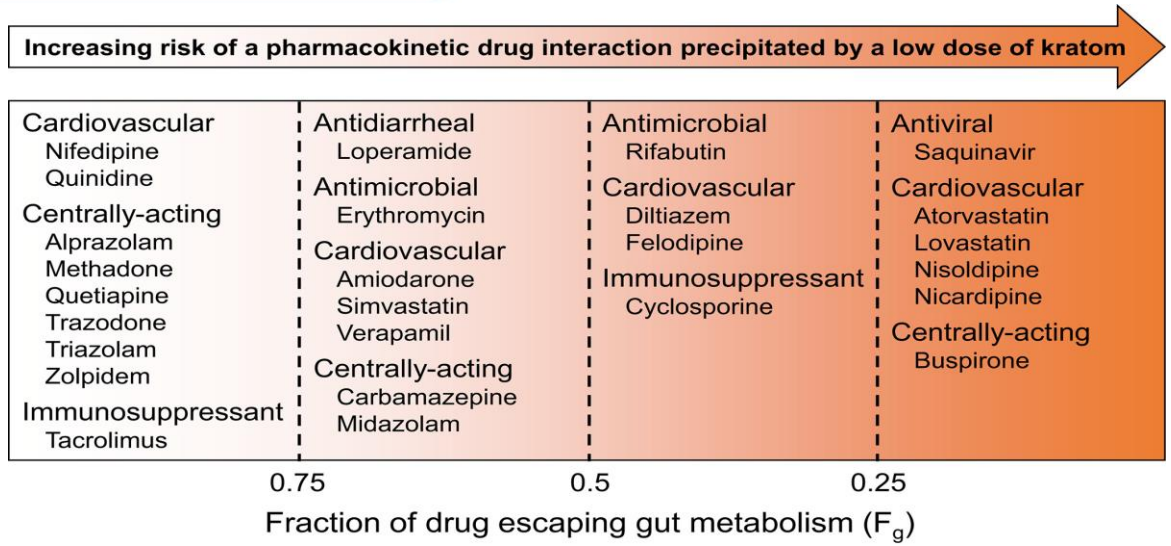
Potential DDIs with Kratom

- Both pharmacokinetic and pharmacodynamic drug interactions are possible/probable with kratom use:
  - Additive effects possible with other CNS sedative drugs (alcohol, benzodiazepines, barbiturates, opioids)
  - Mitragynine is a strong inhibitor of CYP2D6 at concentrations found in plasma
  - Mitragynine, 7-hydroxymitragynine, and other alkaloids are mild to moderate inhibitors of CYP2C9 and CYP3A4
  - Unknown etiology of liver toxicity in reported cases, potentially associated with specific kratom products?
- Variability of kratom products and non-GMP regulation makes it difficult to determine actual content of products, consider recommending GMP products (less adulteration, tested for metals and microbial contamination, see American Kratom Association)

Potential DDIs with Kratom

1. Inhibition of intestinal CYP3A at low kratom dose
2. Inhibition of intestinal P-gp at low kratom dose
3. Inhibition of hepatic CYP3A and CYP2D6 at higher kratom dose





Source(s): Drug Metab Dispos. 2023 Aug;51(8):923-935.
Clin Pharmacol Ther. 2023 Jun;113(6):1315-1325.

Kratom Use Disorder Symptoms per DSM-5

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

	Full Sample (N = 2061)		KUD (n = 525)		No KUD (n = 1536)		*P**
Sample Characteristics	**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 (2-3 SUD symptoms)	—	—	347	66.1	—	—	
Moderate (4-5 SUD symptoms)	—	—	105	20.0	—	—	
Severe (≥6 SUD symptoms)	—	—	73	13.9	—	—	

* *P* value is for chi-square test, comparing KUD with no KUD.
KUD indicates kratom use disorder.

Source(s): J Addict Med. 2024 Mar 5

Case studies – Kratom Use Disorder

- Several case studies report dependence on kratom
  - 3 cases of kratom dependence were treated with buprenorphine/naloxone in Veterans with prolonged polysubstance use (Lei et al., *Subst Abus*, 2021)
  - Kratom dependence, presenting primarily as anxiety and dysphoria, was treated with TCA clomipramine (Vento et al., *Front Psychiatry*, 2021)
  - Kratom dependence in chronic pain patient with symptoms of worsening anxiety, depression, and pain was treated with buprenorphine/naloxone (Bowe & Kerr, *J Psychoactive Drugs*, 2020)
  - Kratom Use Disorder comorbid with ADHD treated with buprenorphine/naloxone in college-aged student (Schmuhl et al., *Subst Abus*, 2020)
- Not all cases may require medication-assisted treatment, dose reduction to mitigate withdrawal symptoms over 14-21 days may work for some users
- Current best practice for KUD: outpatient treatment titrating with buprenorphine ± naloxone (usually requires lower dose than opioids)

Kratom Use Disorder – Dose vs. Frequency

Self-reported Kratom Use Disorder Symptoms	Standardized Dose Amount (z-score)	Dose Frequency (Kratom Doses/ Day)	Female sex		
	OR [95% CI]	OR [95% CI]	OR [95% CI]	Pseudo R2	Cohen d
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

Source(s): Drug Alcohol Depend. 2024 May 20:260:111329.

Kratom Use – Self-reported beneficial effects

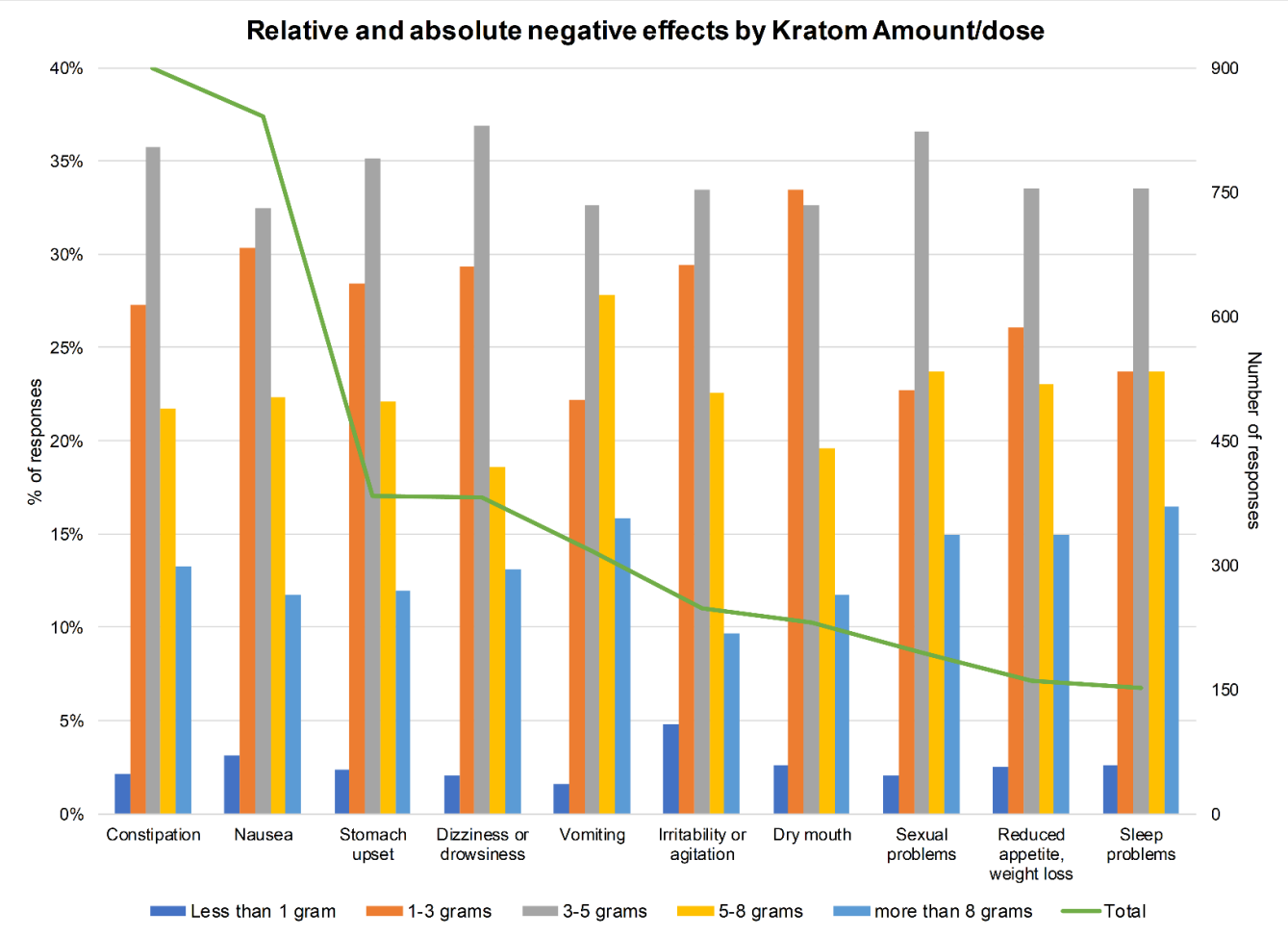
Table 4
Self-reported perceived beneficial effects of Kratom use. Odds ratios (OR), 95% Confidence Intervals (CI), and number of respondents (N) for each level grouped by amount/dose and doses/week. Binomial logistic regression was used. Values in italics indicate significant differences ($p < 0.05$) to reference group.

Predictor	N	Increased energy		Decreased pain		Increased focus		Less depressive mood		Less anxious mood		Reduced or stopped the use of opioid painkillers		Reduced PTSD symptoms		Elevated mood		Other	
		Yes: 6394, No: 1241		Yes: 6466, No: 1139		Yes: 5299, No: 2306		Yes: 6084, No: 1521		Yes: 5978, No: 1627		Yes: 3715, No: 3890		Yes: 1300, No: 6305		Yes: 5790, No: 1815		Yes: 1227, No: 6378	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Amount of Kratom per dose																			
Less than 1 g	504	*0.58*	0.40–0.83	1.12	0.77–1.61	0.86	0.64–1.16	*0.48*	0.34–0.68	*0.67*	0.49–0.92	*0.63*	0.48–0.84	1.17	0.82–1.66	*0.53*	0.39–0.73	0.79	0.56–1.11
1–3 g	3094	0.84	0.61–1.14	1.15	0.86–1.55	1	0.79–1.28	*0.67*	0.50–0.91	0.94	0.72–1.23	*0.72*	0.57–0.91	0.97	0.72–1.29	*0.76*	0.59–0.99	*0.65*	0.49–0.85
3–5 g	2487	0.92	0.67–1.26	1.14	0.85–1.54	1.01	0.80–1.29	0.8	0.59–1.08	1.11	0.85–1.46	*0.75*	0.59–0.94	0.97	0.72–1.30	1.07	0.82–1.40	0.76	0.58–1.01
5–8 g	1160	0.97	0.69–1.37	1.25	0.90–1.74	1.07	0.83–1.39	1.05	0.76–1.46	1.11	0.82–1.48	0.88	0.69–1.12	1.01	0.74–1.38	1.25	0.93–1.68	0.8	0.59–1.07
more than 8 g (reference)	360																		

N=8,049

Source(s): Drug Alcohol Depend. 2017 Jul 1:176:63-70.

Kratom Use – Self-reported detrimental effects



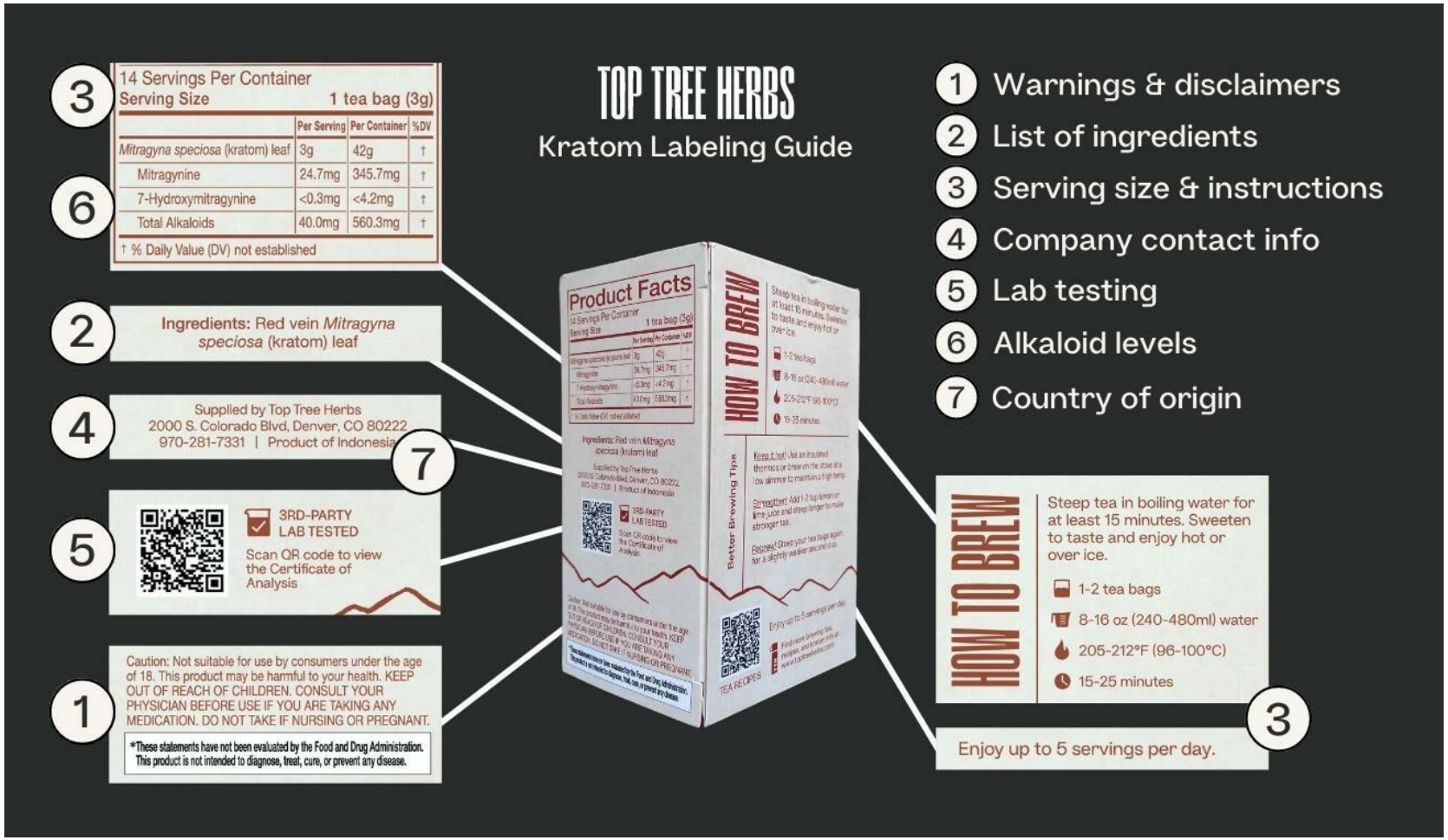
N=5,152

Source(s): Am J Drug Alcohol Abuse. 2022 Jul 4;48(4):433-444.

Current clinical practice recommendations

- Kratom as self-treatment
  - Evaluate drug interactions (CYP3A and 2D6)
  - Avoid other CNS active drugs
  - Not intended to replace any other medication
- Product recommendation
  - Native kratom leaf material (pre-clinical and clinical study results)
  - Labeling according to KCPA
- Dosing
  - Low amounts (1 g) to see effect, only dose to amount needed for intended use

KCPA compliant Kratom label



Source(s): https://toptreeherbs.com/kratom-lawsuits-space-dust-labeling/

Conclusions

- Kratom has been used as a traditional medicine for centuries to self-treat fatigue, pain, diarrhea, and other disorders
- Kratom alkaloids act on multiple receptors, not a classical opioid
- Use in the US in diverse formulations, native leaf material closest to traditional use
- May benefit consumers with pain, psychiatric conditions, fatigue, sleep disorders, and as a harm reduction agent
- KUD is possible with higher doses and more frequent use but withdrawal usually mild
- Buprenorphine ± naloxone has been reported in cases of KUD
- Recommendations to consumers: adequate label, consult with healthcare professional, do not take if other CNS active drugs, do not take when pregnant or nursing

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Thank you

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