ECHO IDAHO

Opioids, Pain and Substance Use Disorders

Kratom & Kava

May 8, 2025

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None of the planners or presenters for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

University of Idaho
School of Health and Medical Professions

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Learning Objectives

- Understand the basic pharmacologic activity of both kratom and kava
- Recognize different clinical settings in which patients may consider using kratom and kava
- Describe the risks associated with use of both kratom and kava

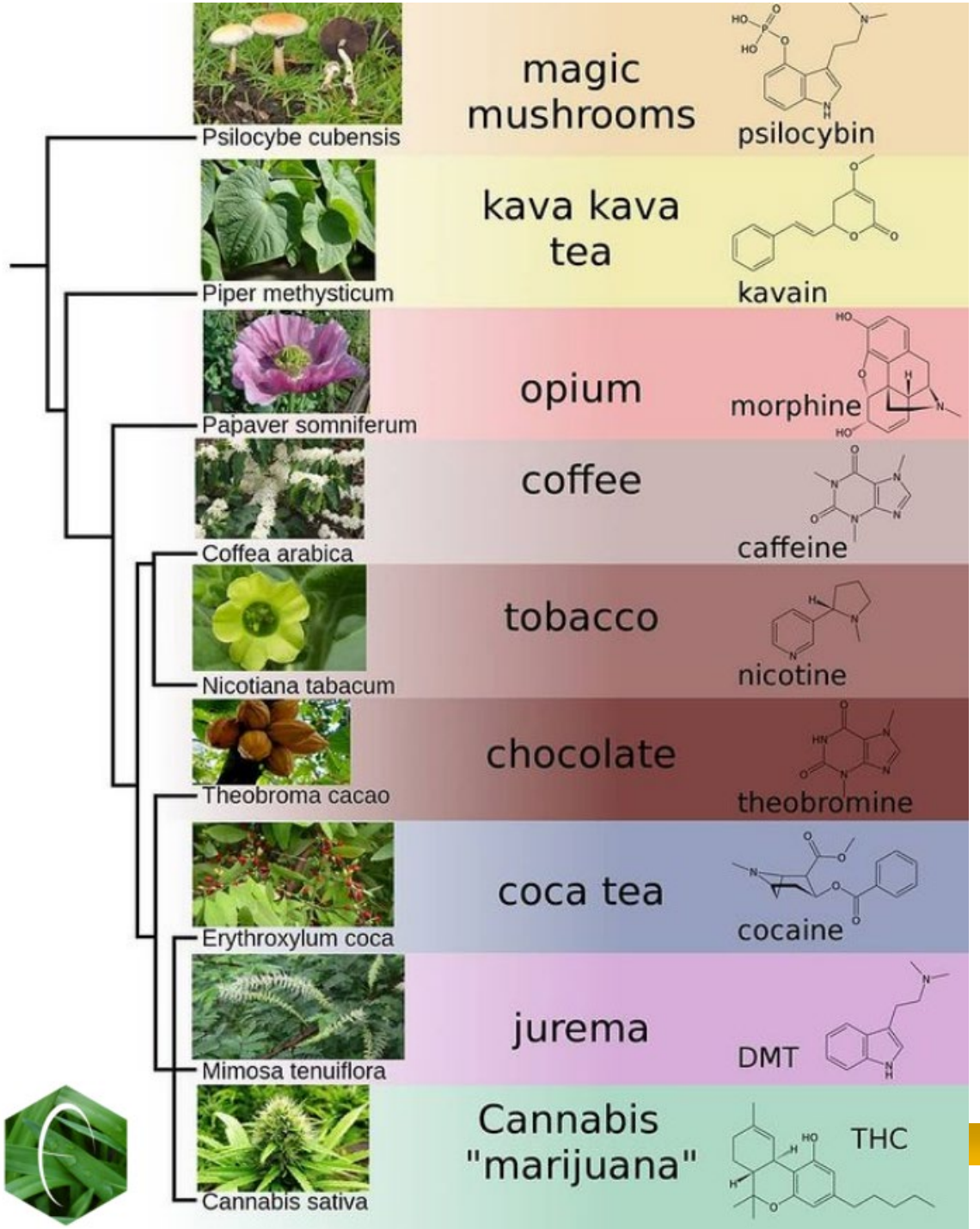


Image: Psychoactive Plants - Psychoactive plant - Wikipedia

Behind the bar, Carlee Palermo, 25, keeps the kratom coming. She says she drinks the tea to help with a degenerative condition in her spine: "It completely took away my back pain."

The customers tonight at Kavasutra say they aren't aware of anyone who has been harmed by kratom. Then Palermo spills a little tea: Many of the people who come to the bar are in recovery from substance abuse.

Asked whether kratom helps with that, she says, "One hundred percent. It's done nothing but help anybody that I've seen."

npr.org/2023/07/08/1186514144/kratom-herbal-supplement-lawsuits-deaths-fda

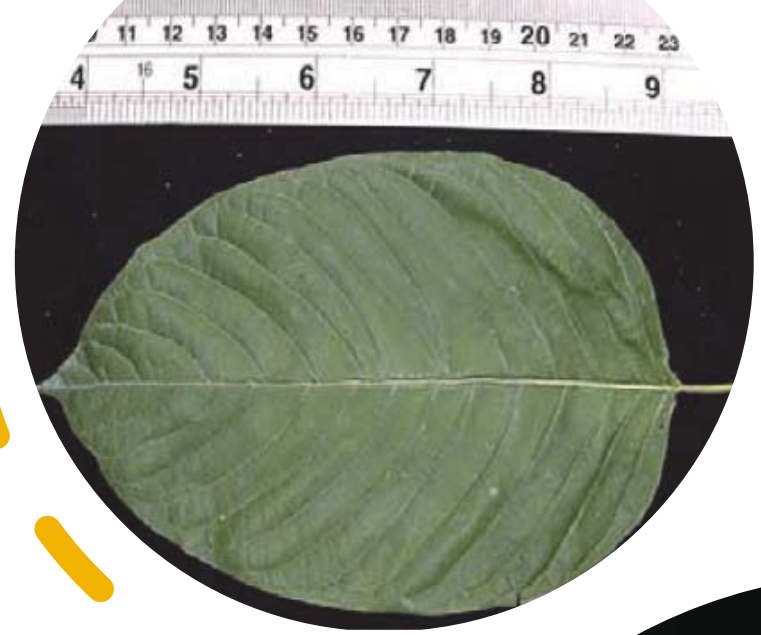
KRATOM

Mitragyna speciosa

Image: https://www.sociedelic.com/kratom-weapon-drug-addiction-withdrawal-natural-remedies/

Origins of Kratom

- Species: Mitragyna speciosa
  - Biologically active alkaloids:
    - Mitragynine 66%
    - Paynantheine 9%
    - Speciogynine 7%
    - 7-hydroxymitragynine 2% **
    - Speciophylline 1%
- Appearance leaf form: See right
  - Mitragynine isolated: white amorphous powder, soluble in ETOH, chloroform, acetic acid
  - Drank as tea, liquid extract, powder in capsules
- Origin: Tropical evergreen tree native to Indonesia, Thailand, and Myanmar
  - Tree reaches heights of 50 feet; spread of 15 feet
  - Member of the Rubiaceae family (Coffee!)
- Common names: Kratom, thang, kakuam, thom, ketum, biak



Swogger M, et al. *Drug & AlcDep. 2016.*
DEA Drug Fact Sheet: Kratom

Uses of Kratom

- Multiple varying rationales: analgesia, anxiolysis, attenuation of opioid withdrawal symptoms, weight loss, energy, sleep

- Routes of administration:
  - Oral ingestion
  - Leaves are dried or powdered, crushed and then smoked, brewed with tea, or placed in gel capsules, tablets, extracts
  - Kratom leaf may be chewed

- Different colors of veins on leaves = differing potencies???

- Purchased over internet and in smoke shops, gas stations, tea shops, bars, other boutique shops
  - Chopped leaves, capsules, compressed tablets, concentrated extracts

Swogger M, et al. *Drug & AlcDep. 2016.*
DEA Drug Fact Sheet: Kratom
Image: vietrealm.com

Examples of Kratom Commercially Available Products

https://www.brothersbotanicals.com/Premium-Kratom-Capsules-Mitragyna-Speciosa-50-Count_p_23.html

MAYO CLINIC

Healthy Lifestyle

Consumer health

Users swear by kratom for mood enhancement and fatigue reduction, but safety issues and questions abound.

If you read health news or visit vitamin stores, you may have heard about kratom, a supplement that is sold as an energy booster, mood enhancer, pain reliever and antidote for opioid withdrawal. However, the truth about kratom is more complicated, and the safety problems related to its use are concerning.

Nearly **2 million people** aged 12 and older used kratom within the past year, according to a 2022 federal estimate

https://www.mayoclinic.org/healthy-lifestyle/consumer-health/in-depth/kratom/art-20402171?p=1
https://www.samhsa.gov/data/sites/default/files/reports/rpt42731/2022-nsduh-nnr.pdf

Pharmacologic Effects

- Onset: within 5-10 minutes
- Duration: 2 to 5 hours
- Dose-dependent effects:

Low doses → stimulant-like (1-5 grams)

- Stimulant effects, increased alertness, physical energy, talkativeness

High doses → opioid-like (>5 grams)

- Sedation; Euphoria
- 630g dose = drug-liking of 5mg IV morphine

- Adverse Effects
  - Nausea, itching, sweating, dry mouth, constipation, increased urination, tachycardia, vomiting, drowsiness
  - Anorexia, insomnia, hepatotoxicity, hallucinations

1 The begining

The stimulating and mode boosting effects are subtle but noticaeble

Mild 2

You can definitely feel the moodboosting and stimulating effects

3 Moderate

In this level there is a balance between stimulation,euphoria,sedation and pain killing effects

Strong 4

The effects are sedative,euphoric and very analgesic.

5 Very strong

Most people cant handle this stage. The sedative effects are substantial and the euphoria can cause hallucinations

Images: Nootroholic.com
https://images.app.goo.gl/kv5HpYrjoke4Y2TX6

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Pharmacologic Action

Kratom alkaloids (>40 types)

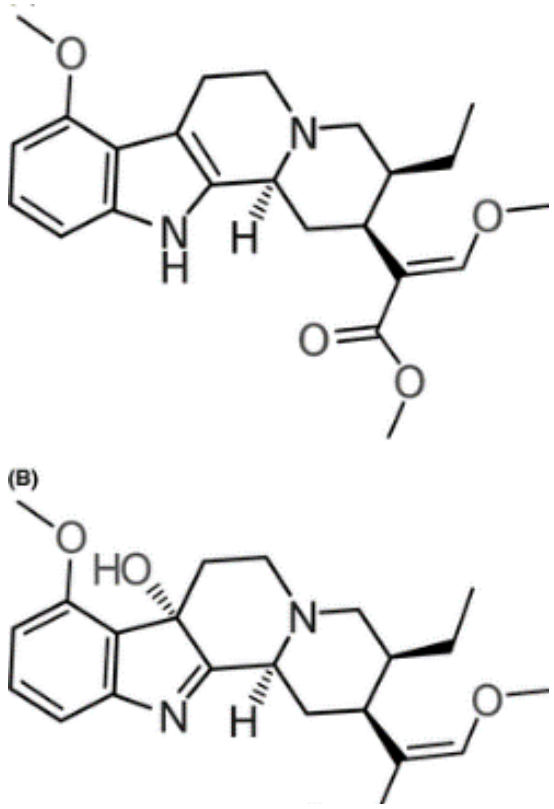
Non-Opioid Activity

- α-2 adrenergic agonism
- Potential 5HT2a-related action

Opioid Pharmacology

- MG and 7-OH-MG bind to OR
- MOR > DOR & KOR

COX-2 mRNA inhibition



White CM. Am J Health-Syst Pharm. 2017; 74:e589-95
Swogger M, et al. *Drug & AlcDep. 2018.*

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Pharmacokinetics

- In vitro, kratom extract was found to inhibit the following CYP P-450 isoenzymes:

2C9 → 2D6* → 1A2 → 3A4

**most potent inhibition*

- Using CYP system to boost effects via the “4 x 100” cocktail (common in adolescent population in Thailand):
  - Kratom leaves are boiled and mixed w/caffeine soda, dextromethorphan, codeine
  - + diphenhydramine (CYP2D6 inhibitor)

Am J Health-Syst Pharm. 2017; 74:e589-95
Swogger M, et al. *Drug & AlcDep. 2018.*
Image: http://img.medscapestatic.com/pi/features/slideshow-slide/drug-abuse-manifestations/updated/fig2.jpg?resize=645:439

Pharmacokinetics

- Reminder: Rule of Five

- 5x the t ½ = the time at which the drug is "completely" (97%) eliminated from the body

- 1x ½ life = 50% original drug removed
- 2x ½ life = 75%
- 3x ½ life = 87.5%
- 4x ½ life = 93.75%
- 5x ½ life = 98.875%

RAT DATA:

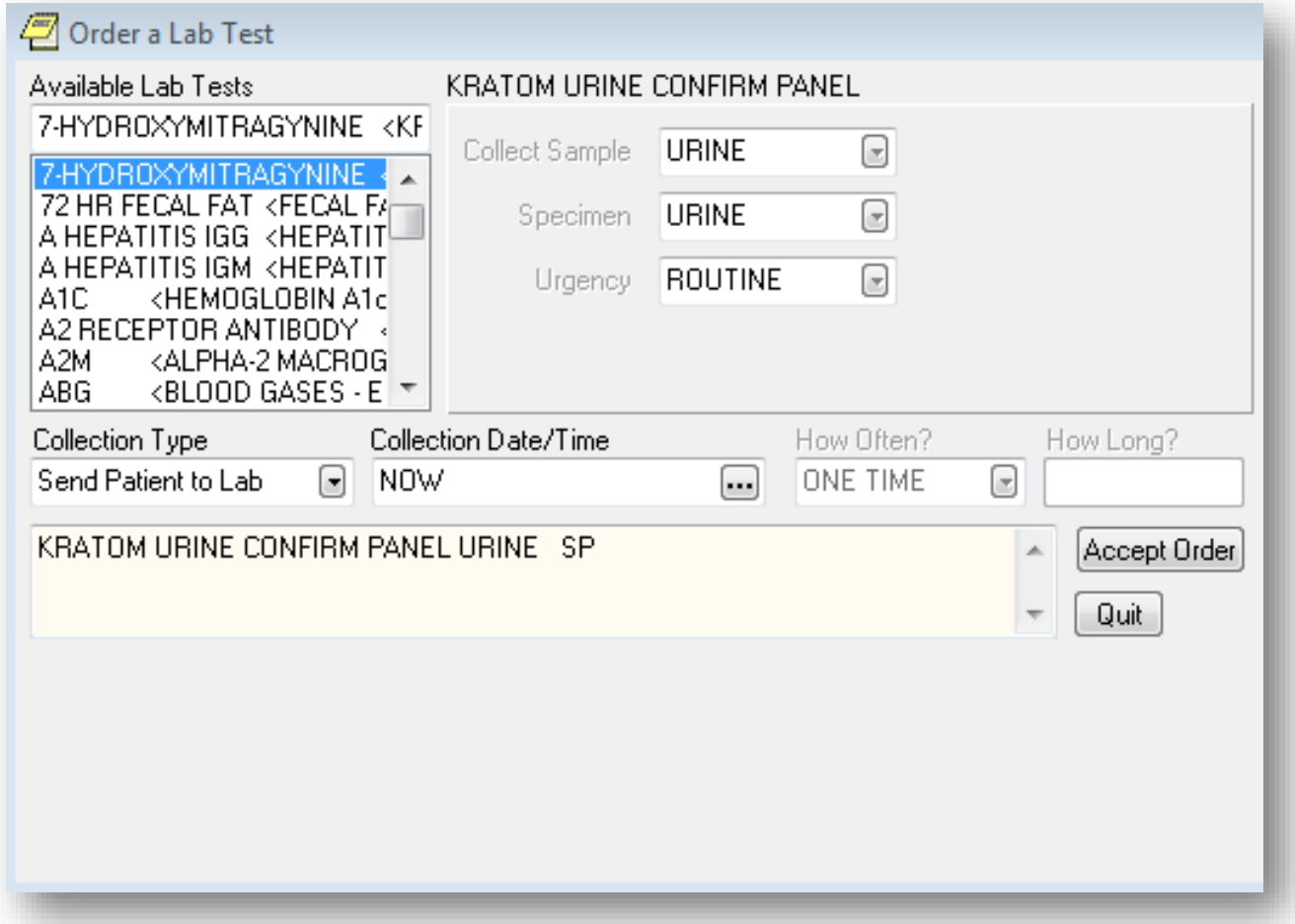
TMAX: 1.2 – 1.8 H
T ½: 3.9 – 9.4 H
VD: 37.9 – 89.5 L/KG

AVAILABLE HUMAN DATA: (SMALL STUDIES)

TMAX: 0.83 ± 0.35 H
T ½: 23.24 ± 16.07 H
VD: 38.04 ± 24.32 L/KG

Raffa, et al. *J Clin Pharm Ther*. 2018; 43: 437– 441
White CM. Am J Health-Syst Pharm. 2017; 74:e589-95

Laboratory Detection



PROVIDER INSTRUCTIONS:

1. If positive, this panel test will quantify the following:
   - 7-HYDROXYMITRAGYNINE
   - MITRAGYNINE

*A cost of $78.50 will incur if either of the above is performed.

2. This test request 30 mLs (NLT 20) of urine.

Test Code: 791750

TAT: 6 - 11 Days

PROCESSING INSTRUCTIONS:

1. This test requires 30 mLs (NLT 20) REFRIG, Random Urine.

Please make two aliquots, one to send using the LabCorp Aliquot Tube and one backup aliquot (reserve the Primary cup if possible) and store in the walk-in.

Kratom Withdrawal Symptoms

- Withdrawal can be difficult to manage and serious

Hostility, Aggression, Emotional Lability

Physical Opioid Withdrawal Symptoms

Seizures and Death*

Adjunctive medications for management of uncomplicated kratom withdrawal	
Withdrawal Symptoms:	Clonidine 0.1mg q6h PRN 0.1MG PO Q2H PRN FOR KRATOM/OPIOID WITHDRAWAL - COWS >8 0.2MG PO Q2H PRN FOR KRATOM/OPIOID WITHDRAWAL - COWS >12 (Hold for SPB <90 or Pulse <56: MAX DOSE=0.6mg/24hours)
Anxiety, dysphoria, lacrimation, rhinorrhea:	Hydroxyzine 25-50mg TID PRN
Myalgias:	NSAIDS, APAP, methocarbamol 500-1500mg TID PRN
Sleep disturbance:	Trazodone 50-100mg or gabapentin 300-1800mg PRN
Nausea:	Promethazine, ondansetron, prochlorperazine
Diarrhea:	Loperamide 4mg then 2mg after each loose stool; max 16mg/day Bismuth subsalicylate 524mg q30min-1hr; max 4192/day
GI Cramping:	Dicyclomine 10-20mg q6-8hrs PRN

White CM. Am J Health-Syst Pharm. 2017; 74:e589-95
DEA Drug Fact Sheet: Kratom
VA Academic Detailing: Pain Management

Kratom Withdrawal Management

Table 1. Pharmacologic Effects of Kratom From Human Trials[2,6,9,13,20,21,24-34,a]

Adverse Events	Therapy for Adverse Events	Withdrawal Effects	Therapy for Withdrawal
Tachycardia and hypertension	Benzodiazepines, negative chronotropic drugs	Agitation and anxiety	Benzodiazepines, α-2 agonists
Nausea and constipation	Antiemetics, laxative plus stool softener	Abdominal pain and diarrhea	Nonopioid antidiarrheals
Confusion and hallucinations	Benzodiazepines, naloxone	Limb muscle spasms	Benzodiazepines
Seizures	Benzodiazepines, naloxone, anticonvulsants	Joint and muscle pain	Nonopioid pain relievers
Sedation	Naloxone	. . .	. . .

[a]Treatments for adverse events and withdrawal are general treatment suggestions and were not studied in any clinical trials of kratom.

White CM. Am J Health-Syst Pharm. 2017; 74:e589-95
Image: https://images.app.goo.gl/kv5HpYrjoke4Y2TX6

Kratom Dependency

- Kratom Use Disorder (Unofficial….)
  - Often using OUD Criteria for diagnosis
- No guidelines or approved pharmacotherapies for KUD (OUD) available
- Gradual taper recommended for discontinuation
- Multiple case reports demonstrate efficacy with buprenorphine/naloxone for maintenance therapy
  - Doses up to 24mg/6mg daily appear to be effective
  - May be beneficial for comorbid pain
- Methadone and naltrexone may also be considered
  - Considerations for comorbidities and logistical issues

Swogger MT, et al. Understanding kratom use: a guide for healthcare providers. *Front Pharmacol*. 2022;13:801855.
Shah K, et al. Kratom: an emerging issue and need for regulations in the United States. *Prim Care Companion CNS Disord*. 2021;23(1):20r02770.
Prozialeck WC, et al. Kratom use within the context of the evolving opioid crisis and the covid-19 pandemic in the united states. *Front Pharmacol*. 2021;12:729220.
Eastlack SC, Cornett EM, Kaye AD. Kratom-pharmacology, clinical implications, and outlook: a comprehensive review. *Pain Ther*. 2020;9(1):55-69

Kratom Toxicity and Overdose

Toxicity

- Clinical presentation: sedation, constricted pupils (miosis), sweating, dry mouth, nausea, respiratory depression
- Supportive management depending on involved organ system
  - i.e., N-acetyl-cysteine for acute hepatitis; anti-epileptics for seizures, etc.

Overdose

- Efficacy of reversal agents for kratom overdose overall unknown
- Naloxone has not been demonstrated to be highly efficacious (has not been clinically studied)

Shah K, et al. Kratom: an emerging issue and need for regulations in the United States. *Prim Care Companion CNS Disord*. 2021;23(1):20r02770.
Prozialeck WC, et al. Kratom use within the context of the evolving opioid crisis and the covid-19 pandemic in the united states. *Front Pharmacol*. 2021;12:729220.
Gorelick DA. Kratom: substance of abuse or therapeutic plant?. *Psychiatr Clin North Am*. 2022;45(3):415-430.
Eastlack SC, et al. Kratom-pharmacology, clinical implications, and outlook: a comprehensive review. *Pain Ther*. 2020;9(1):55-69

Risks of Kratom Use

2011-2017, National Poison Control Center received **>1800 calls** concerning exposure to kratom

CDC analyzed data from the State Unintentional Drug Overdose Reporting System (SUDORS) to determine impact from July 2016-December 2017

July 2016-June 2017

- Kratom listed as a cause of death in 11 states

July 2017 – December 2017

- Kratom listed as a cause of death in 27 states

The CDC's latest analysis from state overdose fatality records (request of Washington Post) found that kratom was implicated in fatal cases in **44 states and D.C. from 2020-2022:**

- 2022: 846 fatal overdose cases (Sole substance attributed to death in 56)
- 2021: 834 fatal overdose cases (Sole substance attributed to death in 68)
- 2020: 663 fatal overdose cases (Sole substance attributed to death in 58)

Olsen EO, O'Donnell J, Mattson CL, Schier JG, Wilson N. *Notes from the Field:* Unintentional Drug Overdose Deaths with Kratom Detected — 27 States, July 2016–December 2017. MMWR Morb Mortal Wkly Rep 2019;68:326–327. DOI: http://dx.doi.org/10.15585/mmwr.mm6814a2
https://www.washingtonpost.com/health/2024/02/20/kratom-deaths/?_pml=1

Kratom Legal Debate

- Reports of use date back to mid-1800s
- **Most clinicians had not heard of kratom prior to 2016**
  - DEA announced plan for temporary Schedule I status in August 2016
  - Scheduling withdrawn in October 2016 due to public outcry
- FDA has not approved Kratom for any medical use

"The **American Kratom Association**, the largest kratom advocacy group in the United States, helped spur an outpouring of public comments. In response, the DEA put a hold on its scheduling plans"

American Society for Biochemistry and Molecular Biology

Image: kratommarchdc.com; americankratom.org
http://www.asbmb.org/asbmbtoday/201706/Features/KRATOM/

Kratom Le

- Reports of use date
- **Most clinicians h**
  - DEA announc
  - Scheduling
- FDA has not a

AMERICA
KRATOM
ASSOCIATION

American

The kratom industry generated
$1.3 billion
in sales in 2019

- LAPPA 2022

Image: kratommarchdc.com; americankratom.org
http://www.asbmb.org/asbmbtoday/201706/Features/KRATOM/

Kratom Current Legal Status

DEA delayed ruling on scheduling of kratom and listed as “Drug and Chemical of Concern”

- Risk of abuse, contaminated product, seizures upon withdrawal, neonate dependence issues, drug interactions?, liver injury, etc.

Not controlled under Federal Controlled Substances Act

- **KRATOM BANS (January 2025):** Alabama, Arkansas, Indiana, Rhode Island, Vermont, Wisconsin
- **KRATOM REGULATIONS (Mixed levels):** California, Illinois, Louisiana, Minnesota, Mississippi, Nevada, South Dakota, Tennessee, Texas, Virginia, and West Virginia
- Globally, kratom is illegal or restricted in more than a dozen countries, including parts of Europe, Japan and Russia

Kratom Consumer Protection Act

- Multiple states are considering regulating the substance under the "Kratom Consumer Protection Act," or the KCPA. Lobbying efforts to change state bans into KCPAs continue
- **KCPA enacted:** Arizona 2019, Colorado 2022, Florida 2023, Georgia 2019, Oklahoma 2021, Utah 2019,
- During 2023 and 2024, **33 states introduced legislation** related to kratom

Federal Legislation

- **No legislation introduced in House or Senate since 2023 as of May 2025**

Kratom-Summary-of-State-Laws.pdf (legislativeanalysis.org)
LSB11082 (congress.gov)
Kratom-Fact-Sheet-FINAL.pdf (legislativeanalysis.org)

Legality Resources

- LSB11082 (congress.gov)
- Kratom-Fact-Sheet-FINAL.pdf (legislativeanalysis.org)
- Kratom-Summary-of-State-Laws.pdf (legislativeanalysis.org)

Congressional Research Service
Informing the legislative debate since 1914

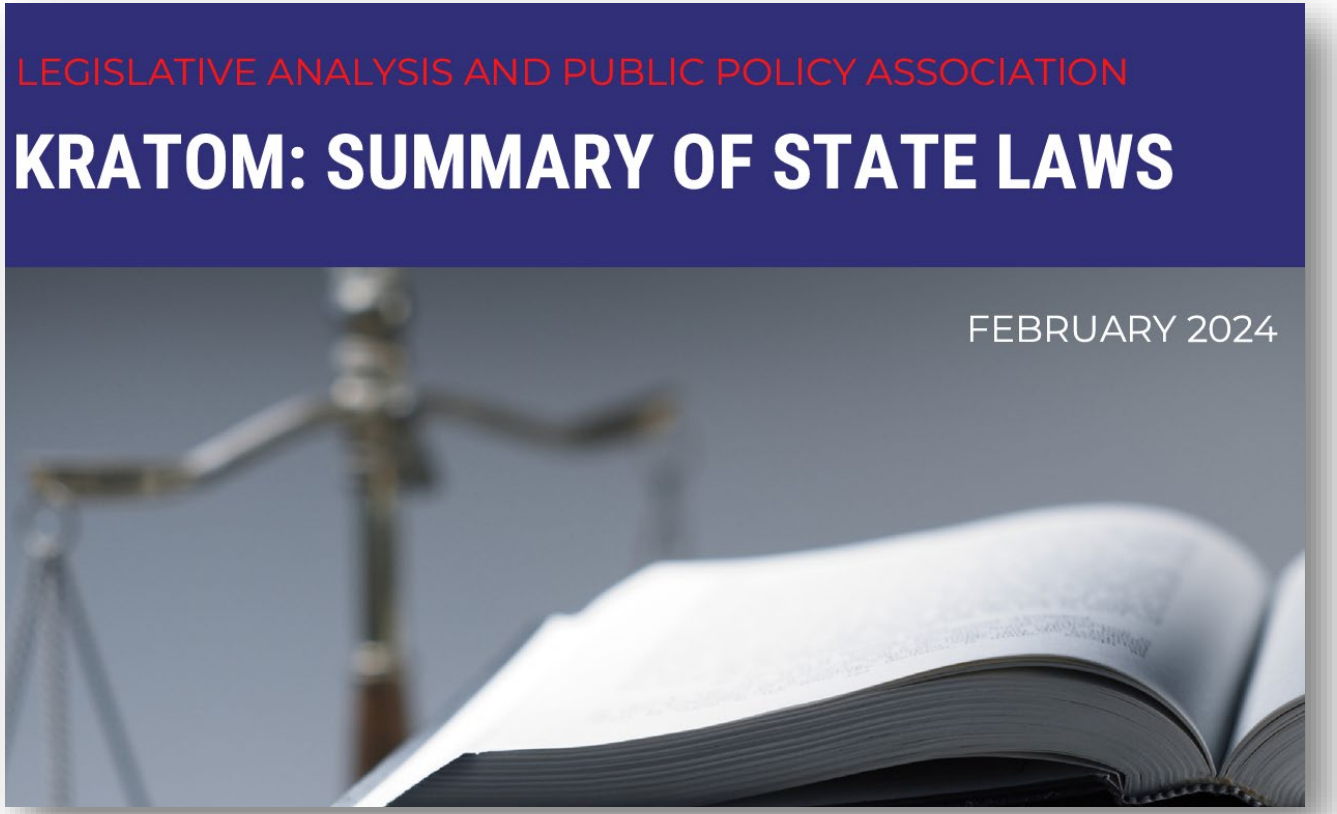
Legal Sidebar

Kratom Regulation: Federal Status and State Approaches

November 28, 2023

Kratom, or *Mitragyna speciosa*, is a tree related to the coffee plant and is native to parts of Southeast Asia. Peoples indigenous to the tree's range have traditionally consumed the leaves of the tree for medicinal and other purposes. Users report both stimulant and sedative effects, believed to be caused by two compounds in the leaves, mitragynine and 7-hydroxymitragynine. Some commentators have raised safety concerns over kratom use, while others have suggested various beneficial uses. Additionally, some kratom products intended for sale in the United States have been found to contain dangerous contaminants, such as salmonella and heavy metals.

Kratom use in the United States has reportedly become more widespread in the past decade, and its regulatory status has been a matter of recent debate. This Sidebar begins by reviewing federal administrative actions relating to kratom before summarizing kratom-focused bills introduced in the current Congress. The Sidebar then describes the various approaches taken by 22 states that have regulated or banned kratom, which may be instructive as Congress considers action on kratom.



The New York Times

Opioid Users Call Kratom a Godsend. The F.D.A. Says It's a Menace.

npr

HEALTH

Herbal supplement kratom targeted by lawsuits after a string of deaths

https://www.nytimes.com/2019/04/17/us/kratom-overdose-deaths.html
https://www.npr.org/2023/07/08/1186514144/kratom-herbal-supplement-lawsuits-deaths-fda

Kratom Legal Action

- April 2023: U.S. Marshals, at the FDA's request, seized more than 250,000 units of dietary supplements and bulk dietary ingredients that are or contain kratom, including over 1000 kilograms of bulk kratom
- Multiple recent wrongful death lawsuits
  - In July 2023, Jury in WA awarded $2.5 mil verdict in first kratom wrongful death trial in US
  - Landmark trial, concentrated kratom extract from Idaho
- 2025 expected to have multiple new cases, rise in litigation attributed to growing recognition of adverse health effects tied to kratom

"When you're selling a drug next to Skittles or energy drinks, you have no means of knowing that you're dealing with something that is exponentially more dangerous than anything else on the shelf."
– NPR article; Atlanta attorney Matt Wetherington

https://www.fda.gov/news-events/press-announcements/fda-roundup-april-28-2023
https://www.npr.org/2023/07/08/1186514144/kratom-herbal-supplement-lawsuits-deaths-fda
https://www.washingtonpost.com/health/2024/02/20/kratom-deaths/

Kava Kava

Piper methysticum

Kava origins

- Common Names: kava, kava kava, ava pepper, ava root, kawa
  - Also colloquially referred to as “Natures Xanax”

- Pharmacologic effect from kavapyrones (aka kavalactones): 3–20% of the dry weight of the root of the plant
  - 18 known kavapyrones - 96% of the biologic activity is attributable to only 6: **kavain**, dihydrokavain, methysticin, dihydromethysticin, yangonin, demethylxyyangonin

- Latin Names: *Piper methysticum*
  - Native to western Pacific islands; Member of the pepper family
  - Kava means “bitter plant” in Polynesian
  - Piper Methysticum means “intoxicating pepper” in Latin

- Root of the plant are ground into a paste, mixed with water, strained, then consumed
  - Rhizome and root were historically chewed and then expectorated and covered by water and/or coconut milk to extract kavapyrones

- Background/Social History
  - Pacific islanders used kava for thousands of years as a medicine and for ritual purposes

Kava | NCCIH (nih.gov)

Kava Kava: Benefits, Side Effects and Dosage (healthline.com)

Kava Pharmacology

Blockade of voltage-gated sodium ion channels

Reduced excitatory neurotransmitter release due to blockade of calcium ion channels

Enhanced ligand binding to gamma-aminobutyric acid (GABA) type A receptors

Reversible inhibition of monoamine oxidase B

Reduced neuronal reuptake of norepinephrine and dopamine

Weak MAO-B inhibitor

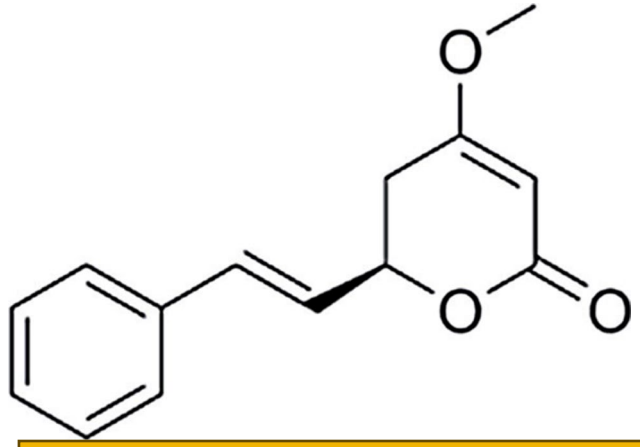
Potentiation of $GABA_A$ activity

NRI

DRI

CB_1

Voltage-gated sodium and calcium channel inhibition



Biologic activity NOT impacted by naloxone or flumazenil

White CM. The pharmacology, pharmacokinetics, efficacy, and adverse events associated with kava. Journal of Clinical Pharmacology. 2018;58(11):1396-1405
Kava: A Comprehensive Review of Efficacy, Safety, and Psychopharmacology - Jerome Sarris, Emma LaPorte, Isaac Schweitzer, 2011 (sagepub.com)

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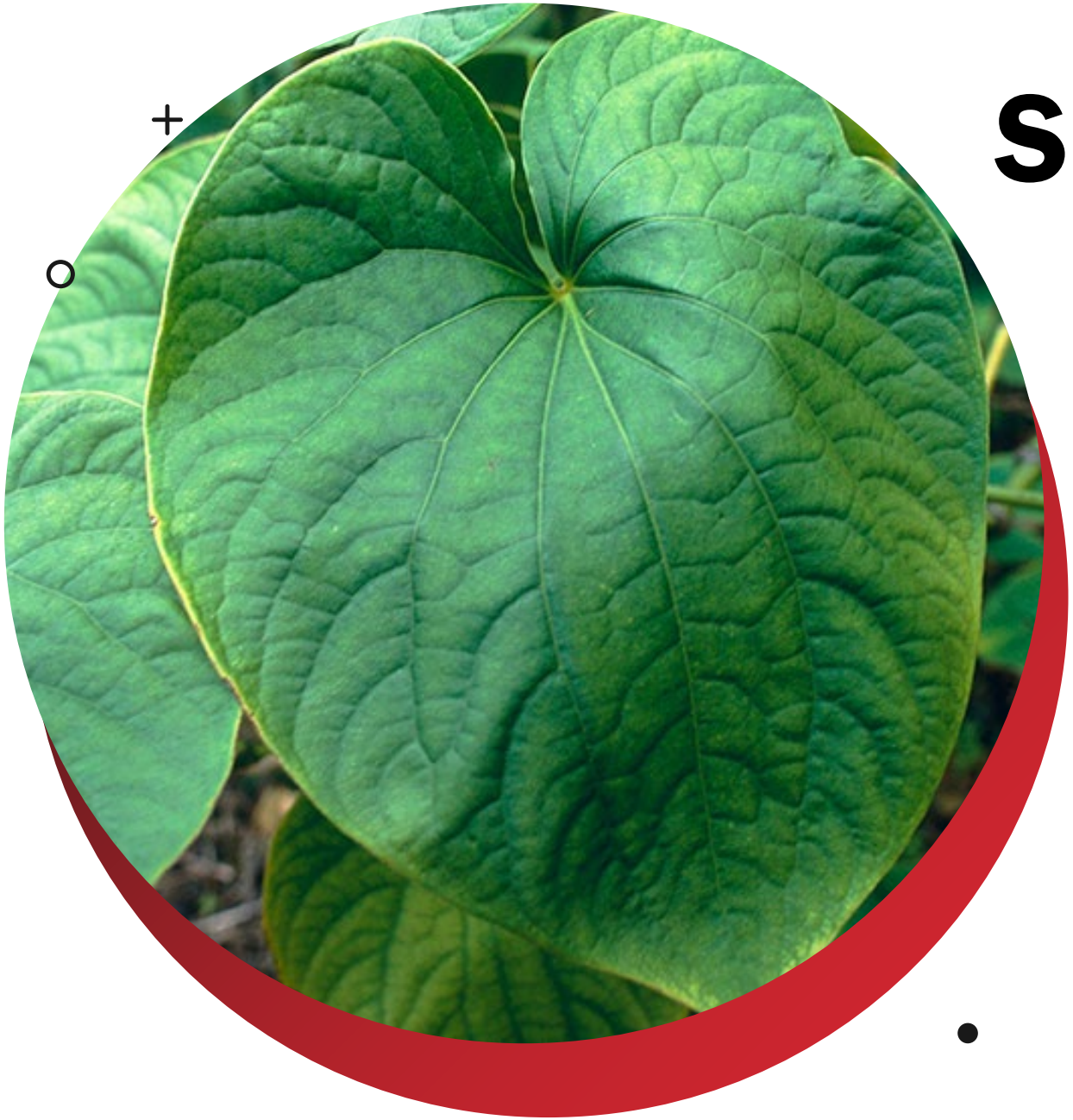
Project ECHO

Kava Modern Uses and Efficacy

- Primary studied indication: Anxiety and Insomnia
  - Other evaluated indications include neuronal damage protection (antioxidative), reduction of pain sensation, PMS, and reduction of cancer (mice)
- Network meta-analysis (Zhang et al 2022) found kava effective as an anxiolytic, but possibly ineffective for GAD
- Anxiolytic effects appear to attenuate over time (not acutely anxiolytic); Anxiety trials evaluated TID dosing
- Found to have good safety profile for short-term use in studies (<6 wks)
  - Compared to standard anxiolytic drugs and found to have low addiction potential when used traditionally, and minimal withdrawal symptoms (Soares 2022)
- Side Effects: headache, dizziness, drowsiness, depression, diarrhea, and occasionally dermatologic manifestations; cessation reversed most of these

White CM. The pharmacology, pharmacokinetics, efficacy, and adverse events associated with kava. Journal of Clinical Pharmacology. 2018;58(11):1396-1405.
Zhang W. Medicinal herbs for the treatment of anxiety: A systematic review and network meta-analysis - PubMed (nih.gov)
Soares RB. An Updated Review on the Psychoactive, Toxic and Anticancer Properties of Kava - PMC (nih.gov)



Suggested Dosing

- Kava supplements may list kavalactones in milligrams or as a percentage
  - *e.g., capsules of 100 mg of kava root extract may be standardized to contain 30% kavalactones = 30mg/capsule*
- Most extracts of kava root contain 30–70% kavalactones
- Suggested dosage for treatment of nonpsychotic anxiety is 105 to 210 mg daily for three to four weeks
- Published evidence of tolerance/withdrawal is limited

Kava Kava - LiverTox - NCBI Bookshelf (nih.gov)
An Updated Review on the Psychoactive, Toxic and Anticancer Properties of Kava - PMC (nih.gov)

Examples of Available Formulations

Kava tea:

Most common method of administration; As previous, from kava root; Sometimes combined with other herbal tea ingredients

Kava capsules, powder, or liquid/tincture:

Made from a concentrated mixture prepared by extracting kavalactones from the root of the plant with ethanol or acetone

Risks of Kava Use

- Route Matters:
  - Moderate consumption in traditional form, i.e., water-based suspension of kava roots, deemed "acceptably low level of health risk" by World Health Organization
  - Consumption of extracts produced with organic solvents, or excessive amounts of poor-quality kava products, may be linked to an increased risk of adverse health outcomes, including potential liver injury
- Abuse Potential
  - Present, yet appears to be low with conventional use
- Liver Toxicity:
  - Mechanism of liver injury is unclear and causality not well shown; LiverTox Likelihood Score; A
  - Kavalactones not intrinsically cytotoxic (although other components of kava preparations may be)
  - In vitro studies find kavalactones inhibit several CYP450 ie
  - Clinical cases of hepatotoxicity due to kava suggest an idiosyncratic or immunoallergic pathogenesis
- CNS Depression
  - Combination with other agents known to cause CNS depression may result in potentiated effects

Image: Kava kava: Uses, benefits, risks, dosage, and interactions (medicalnewstoday.com)
Kava Kava - LiverTox - NCBI Bookshelf (nih.gov)

Kava Legal State

- Since the 1990s, recreational and medicinal use of kava has extended around the world, including increased popularity in European and North American countries
  - After years of general acceptance, there was a backlash in the early 2000s due to cases of hepatic toxicity
  - Canada, Great Britain, Australia, and Germany, have restricted or banned kava kava
- In November 2002, the Food and Drug Administration issued a consumer advisory
- Kava bars are common across the US: serve kava tea (along with kratom, other herbal remedies) instead of alcohol
  - Noted by users to be a helpful tool in sobriety

KARUNA KAVA BAR & BEVERAGE COMPANY

Kava Kava - LiverTox - NCBI Bookshelf (nih.gov)
Karuna Kava Bar | Home
SquareRut Kava Bar - Barton Springs - Check Kava Menu, Reviews & Deals (bestkavabar.com)

Key Points

Kratom

- Pharmacologic effects are dose-dependent, ranging from stimulant- to opioid-like, and include mu-opioid agonism, COX-2 inhibition, among others
- Used for pain, anxiety, sleep, alertness, appetite suppression, withdrawal mitigation, more
- Drug interactions are possible and sometimes used intentionally to amplify effects
- Kratom is known to have a potential for addiction, and is associated with dependence and withdrawal; Withdrawal can be serious and may require medical attention
- Federally legal substance with some state level banning/regulation; Restrictions/banning varies globally

Kava

- Pharmacologic effects result from enhancement of GABAergic activity, without directly binding to GABA (non-BZD-like) and from NDRI activity
- Used primarily for anxiety and sleep
- Drug interactions are possible, both pharmacodynamically and pharmacokinetically
- Kava carries a low but present risk for abuse and potential for addiction; Tolerance and withdrawal are not well documented; Adulteration may increase risk
- Federally legal substance in the United States (restrictions/bans globally)

Image: https://paylesskratom.com/product/krave-kratom-kava-blend-extract-shot/

Questions?

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References

- National Center for Complementary and Integrative Health. Health Information: Kava. National Center for Complementary and Integrative Health website accessed at https://www.nccih.nih.gov/health/kava. April 10, 2024.
- Becker MW, Lourençone EMS, De Mello AF, et al. Liver transplantation and the use of kava: case report. Phytomedicine. 2019;56:21-26.
- Kava kava. LiverTox: clinical and research information on drug-induced liver injury. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2018.
- Kava. Natural Medicines website. Accessed at https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=872 on January 22, 2024.
- Pittler MH, Ernst E. Kava extract for treating anxiety. Cochrane Database Syst Rev. 2003;2003(1):CD003383. doi: 10.1002/14651858.CD003383. PMID: 12535473; PMCID: PMC6999799.
- Sarris J. Herbal medicines in the treatment of psychiatric disorders: 10-year updated review. Phytotherapy Research. 2018;32(7):1147-1162.
- Sarris J, Stough C, Bousman CA, et al. Kava in the treatment of generalized anxiety disorder. A double-blind, randomized, placebo-controlled study. Journal of Clinical Psychopharmacology. 2013;33(5):643-648.
- Smith K, Leiras C. The effectiveness and safety of kava kava for treating anxiety symptoms: a systematic review and analysis of randomized clinical trials. Complementary Therapies in Clinical Practice. 2018;33:107-117.
- White CM. The pharmacology, pharmacokinetics, efficacy, and adverse events associated with kava. Journal of Clinical Pharmacology. 2018;58(11):1396-1405.

References

- Henningfield JE, Fant RV, Wang DW. The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. Psychopharmacology (Berl). 2018 Feb;235(2):573-589. doi: 10.1007/s00213-017-4813-4. Epub 2017 Dec 23. Review. PubMed PMID: 29273821; PubMed Central PMCID: PMC5813050.
- Tatum WO, Hasan TF, Coonan EE, Smelick CP. Recurrent seizures from chronic kratom use, an atypical herbal opioid. Epilepsy Behav Case Rep. 2018 Apr 17;10:18-20. doi: 10.1016/j.ebcr.2018.04.002. eCollection 2018. PubMed PMID: 30062086; PubMed Central PMCID: PMC6063981.
- White CM. Pharmacologic and clinical assessment of kratom. Am J Health Syst Pharm. 2018 Mar 1;75(5):261-267. doi: 10.2146/ajhp161035. Epub 2017 Dec 18. Review. PubMed PMID: 29255059.
- Diep J, et al. Kratom, an Emerging Drug of Abuse: A Case Report of Overdose and Management of Withdrawal. A Case Rep.2017 Oct 26. doi: 10.1213/XAA.0000000000000658. [Epub ahead of print] PubMed PMID: 29077662.
- Fluyau D, Revadigar N. Biochemical Benefits, Diagnosis, and Clinical Risks Evaluation of Kratom. Front Psychiatry. 2017 Apr 24;8:62. doi:10.3389/fpsyt.2017.00062. eCollection 2017. Review. PubMed PMID: 28484399; PubMed Central PMCID: PMC5402527.
- Warner ML, Kaufman NC, Grundmann O. The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. Int J Legal Med. 2016 Jan;130(1):127-38. doi: 10.1007/s00414-015-1279-y. Epub 2015 Oct 28. Review. PubMed PMID: 26511390.
- Tayabali K, Bolzon C, Foster P, Patel J, Kalim MO. Kratom: a dangerous player in the opioid crisis. J Community Hosp Intern Med Perspect. 2018 Jun 12;8(3):107-110. doi: 10.1080/20009666.2018.1468693. eCollection 2018. PubMed PMID: 29915645; PubMed Central PMCID: PMC 5998276.
- Olsen EO, O'Donnell J, Mattson CL, Schier JG, Wilson N. *Notes from the Field:* Unintentional Drug Overdose Deaths with Kratom Detected — 27 States, July 2016–December 2017. MMWR Morb Mortal Wkly Rep 2019;68:326–327. DOI: http://dx.doi.org/10.15585/mmwr.mm6814a2
- Trakulsrichai S, Sathirakul K, Auparakkitanon S, et al. Pharmacokinetics of mitragynine in man. Drug Des Devel Ther. 2015 Apr 29;9:2421-9. doi: 10.2147/DDDT.S79658. eCollection 2015. PubMed PMID: 25995615; PubMed Central PMCID: PMC4425236.
- Raffa, RB, Pergolizzi, JV, Taylor, R, Ossipov, MH. Nature's first "atypical opioids": Kratom and mitragynines. *J Clin Pharm Ther*. 2018; 43: 437– 441. https://doi.org/10.1111/jcpt.12676
- Meireles V, Rosado T, Barroso M, et al. *Mitragyna speciosa*: Clinical, Toxicological Aspects and Analysis in Biological and Non-Biological Samples. *Medicines (Basel)*. 2019;6(1):35. Published 2019 Mar 4. doi:10.3390/medicines6010035
- Eldridge WB, Foster C, Wyble L. Neonatal Abstinence Syndrome Due to Maternal Kratom Use. Pediatrics. 2018 Dec;142(6). pii: e20181839. doi: 10.1542/peds.2018-1839. Epub 2018 Nov 7. Review. PubMed PMID: 30404789.

References

- Prozialeck WC, Avery BA, Boyer EW, et al. Kratom policy: The challenge of balancing therapeutic potential with public safety. Int J Drug Policy. 2019 Aug;70:70-77. doi: 10.1016/j.drugpo.2019.05.003. Epub 2019 May 16. PubMed PMID: 31103778.
- Veltri C, Grundmann O. Current perspectives on the impact of Kratom use. Subst Abuse Rehabil. 2019 Jul 1;10:23-31. doi: 10.2147/SAR.S164261. eCollection 2019. PubMed PMID: 31308789; PubMed Central PMCID: PMC6612999.
- Henningfield JE, Grundmann O, Babin JK, Fant RV, Wang DW, Cone EJ. Risk of death associated with kratom use compared to opioids. Prev Med. 2019 Nov;128:105851. doi: 10.1016/j.ypmed.2019.105851. Epub 2019 Oct 21. PubMed PMID: 31647958.
- Gutridge AM, Robins MT, Cassell RJ, et al. G protein-biased kratom-alkaloids and synthetic carfentanil-amide opioids as potential treatments for alcohol use disorder. Br J Pharmacol. 2019 Nov 8. doi: 10.1111/bph.14913. [Epub ahead of print] PubMed PMID:31705528.
- Kruegel AC, Uprety R, Grinnell SG, et al. 7-Hydroxymitragynine Is an Active Metabolite of Mitragynine and a Key Mediator of Its Analgesic Effects. ACS Cent Sci. 2019 Jun 26;5(6):992-1001. doi: 10.1021/acscentsci.9b00141. Epub 2019 May 29. PubMed PMID: 31263758; PubMed Central PMCID: PMC6598159.
- Ismail I, Wahab S, Sidi H, et al. Kratom and Future Treatment for the Opioid Addiction and Chronic Pain: Periculo Beneficium? Curr Drug Targets. 2019;20(2):166-172. doi: 0.2174/1389450118666170425154120. PubMed PMID: 28443503.
- Davidson L, Rawat M, Stojanovski S, Chandrasekharan P. Natural drugs, not so natural effects: Neonatal abstinence syndrome secondary to 'kratom'. J Neonatal Perinatal Med. 2019;12(1):109-112. doi: 10.3233/NPM-1863. PubMed PMID: 30149482; PubMed Central PMCID: PMC6484255.