Kratom (Mitragyna speciosa): Medicine, Menace or Merchandise?

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*For Identification purposes only. ***No*** agency support intended nor implied.

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1

Presenter Disclosures

Alan Trachtenberg, MD, MPH

(1) The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

No relationships to disclose (retired)

Neither Kratom (Mitragyna speciosa) nor any of its alkaloids are approved for any human or animal use in the USA. ***All*** discussions in the presentation are of "Off-label (unapproved) use of substances not approved in the United States."

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Introduction

- Kratom *(Mitragyna speciosa)* is a tropical tree
  - AKA Ketum, BiBiak, Biak-Biak, Thang, Kakuam, Thom, Kakuam, Kraton, Ithang
- Native to Southeast Asia (Thailand, Malaysia, Indonesia)
- Belongs to the "coffee family" (*Rubiaceae*)
- M. speciosa is the only Mitragyna species found, so far, to contain opioid alkaloids
- Traditionally used as opium substitute or to treat withdrawals, cough, diarrhea, muscle pain, hypertension
- Kratom is one of many purportedly psychoactive herbals available online, (and advertised in *High Times*) however, this one ***is*** really psychoactive.
  - But as always, little is known about specific chemical entities or combinations of chemicals present in commercially available but unregulated products
- Use and abuse of all these substances is difficult to measure; anecdotal reports found on websites, chat forums, case reports.

J. Diet. Supp. 2013, 10(2):152-70.

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Description

- Tree usually grows 12-30 ft (3.7-9.7 m) tall and 15 ft (4.6 m) wide
- Can be evergreen or deciduous depending on the climate
- Leaves are dark green, can grow over 7 inches long and 4 inches wide with ovate-acuminate shape
- Flowers are yellow and round, tend to grow in clusters at the end of branches

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- Kratom has become increasingly popular as a novel psychoactive substance in Western countries
- Kratom alkaloids bind and activate Mu opioid receptors and appear to have properties that expose users to all usual risks of opioids
- Currently, there are no approved medical uses for kratom.
- **FDA and CDC have received concerning reports about its safety, Including confirmed deaths,**

  A few in which ME reported Kratom as sole Cause of Death (COD)

  Kratom products have been associated with foodborne outbreaks such as salmonella and heavy metal contamination

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Kratom is a botanical that, when in commerce, qualifies as a dietary ingredient under section 201(ff)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321(ff)(1)]. When marketed as a dietary ingredient, FDA also considers kratom to be a new dietary ingredient under section 413(d) of the Act [21 U.S.C. 350b(d)] because, to the best of the agency's knowledge, there is no information demonstrating that this substance was marketed as a dietary ingredient in the United States before October 15, 1994.

In the absence of a history of use or other evidence of safety establishing that kratom will reasonably be expected to be safe as a dietary ingredient, kratom and kratom-containing dietary supplements and bulk dietary ingredients are adulterated under section 402(f)(1)(B) of the Act [21 U.S.C. 342(f)(1)(B)], because they contain a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury.

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Preparation and Consumption

- Leaves typically ingested by chewing, smoking, brewing into tea, or swallowing a tar-like solid
- Lemon juice often added to facilitate extraction
  - Sugar or honey may be added, mix with sweet beverages such as cola
- Mix with cough-syrup (dextromethorphan) to obtain a better "kick"
- Ice-cold cocktail called "4x100" have become popular in southern Thailand
  - Alcohol-mimicking affect, predominantly used by young Muslims
  - Composed of: *M. speciosa* leaves, caffeine-containing soft-drink, and codeine- or diphenhydramine-containing cough syrup.

Neurosci. Biobehav. R. 2013, 37:138-51.
Curr. Top. Med. Chem. 2011, 11(9):1165-75.

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Kratom User Experience Reports

- Claims that *M. speciosa* has opioid and analgesic effects (at higher dose) and stimulant-like effects (at lower dose, but pharmacodynamics unclear)
  (typical opioid reward vs. independent stimulant activity?)
- Regardless method of consumption, produce opium-like effects
- Provides stamina to work
- Feeling happy, strong, and active after 5-10 mins of consumption; effects last several hours
- Typical withdrawal symptoms: hostility, aggression, excessive tearing, inability to work, muscle pain, jerky limb movements
- Long-term users: anorexia, weight loss, insomnia, hyperpigmentation of cheeks
- Common side effects: xerostomia, polyuria, constipation

Neurosci. Biobehav. R. 2013, 37:138-51.
Curr. Top. Med. Chem. 2011, 11(9):1165-75.

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Drug Screening and Analyses

- Kratom and Kratom-derived compounds are not detected in most routine drug testing or screening procedures that find other opioids.
  - report uses HPLC-ESI/MS/MS and GC/MS detection techniques
- No clearly defined drug-level cutoff points
- To be quantitatively meaningful, ***both*** Mitragynine (M) and 7-OH-Mitragynine (7-OH-M) ***must be measured***.
  - **7-OH-M is much more potent, but present in much smaller and highly variable amounts.**
  - **Preparation or storage conditions may INCREASE 7-OH-M and therefore determine total opioid potency**

J. Med. Toxicol. 2010, 6(4):424-6.

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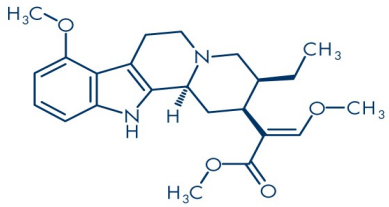
Mitragynine

- First isolated by Hooper in 1907
- Structure fully elucidated in 1965 via X-ray crystallography
- Solubility: acetone, acetic acid, ethanol, chloroform, diethyl ether
- Distillation point: 230-240 °C at 5 mmHg
- Physical appearance: white amorphous crystals
- Melting point: 102-106 °C



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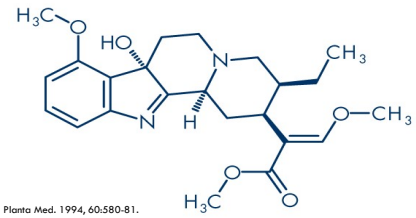
7-hydroxymitragynine

- First identified in 1993
- Solubility: acetone, chloroform, ethanol
- Physical appearance: amorphous powder



Planta Med. 1994, 60:580-81.

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The effects of kratom in humans are dose-dependent:

- Small doses produce stimulatory effects resembling the stimulant effect of drugs such as cocaine or amphetamines.
- Larger dosages associated with sedative-narcotic, pain reducing effects that resemble drugs such as opiates.
- Regular kratom use is associated with addictive disorders, as evidenced by craving and compulsive use. Opioid withdrawal symptoms upon cessation.
- There are wildly varied reports on actual potency of the alkaloids in comparison to Morphine, probably due to the many different types of assays used to measure it, and possibly due to differences in specific effect being measured (is 7-OH-M a biased Mu agonist?)

SOURCE: Prozialeck W. C., Jivan J. K., Andurkar S. V. Pharmacology of Kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. Journal of the American Osteopathic Association. 2012;112(12):792–799; Singh, 2014; Suwanlert, 1975; Ahmad and Aziz, 2012; Vicknasingam et al., 2010; Singh et al., 2014

12

12

History of Use

- *M. speciosa* first described in western literature in early 19th century by Pieter Willem Korthals
  - Official botanist for Dutch East India Service (1831-1836)
- In 1836, reports described *M. speciosa* Korth as a plant that people in Malaysia used when opium was unavailable or unaffordable
- In 1897, reports described *M. speciosa* as a potential cure for opium addiction
- In 1907, descriptions of local methods on how to chew, brew, and smoke Kratom leaves
- In 1921, mitragynine was identified as an active chemical in *M. speciosa*
- In 1930, reports of Kratom use in traditional medicine: ointment and poultice for wounds and as a cure for fevers and diarrhea
- Until recently, use and culture was restricted to Southeast Asia
  - Associated with rural and sub-urban working class
  - Working class social context: Kratom users were considered more desirable workers than cannabis or opium users since the former tended to be more enduring workers, also more desirable as potential husbands since hard work would ensure more financial stability.

J. Diet. Supp. 2013, 10(2):152-70.

13

13

International Control

- **INTERNATIONALLY**
- In 1943, Kratom Act 2486 made *M. speciosa* illegal in Thailand
  - Banned the possession or selling of *M. speciosa* Kratom leaves
  - Required existing cultivated trees to be cut down
  - Claims have been made that it was competing with governmental monopoly on opiates
  - Legal status is now under review:
  - Claim: *"There's never been a single death associated with Kratom. People have been chewing this for thousands of years with no cases of overdose, psychosis, murder, violent crime. Never in all of recorded history." – Pascal Tanguay, program director with Thailand offices of Population Services International (PSI)*
- By 2015 possession was illegal in Australia, Malaysia, Myanmar, and Thailand and
- M. speciosa and/or mitragynine are a controlled drug in Denmark, Poland, Sweden
- Under surveillance in the UK and Germany

Curr. Top. Med. Chem. 2011, 11(9):1165-75.

14

14

Early European Report of Fatalities (2011)

- In Sweden, 9 cases of fatal overdose reported
  - Documented cases over 1 year (November 2009-2010)
  - Ages 22 – 35 y/o, 7/9 males
  - Most found dead at home
  - Autopsy findings: edema and congestion of lungs
- Linked to Krypton
  - Powdered Kratom and *O*-desmethyltramadol
- Post-mortem blood samples contained mitragynine (0.02 – 0.18 mcg/g) and *O*-desmethyltramadol (0.4 – 4.3 mcg/g)
- Blood concentrations of tramadol >1.0 mcg/g are considered toxic and possibly fatal and <u>most of these deaths likely due primarily to Tramadol</u>

J. Anal. Toxicol. 2011, 35(4):242-47.

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Control in North America

- Kratom was legal to grow and purchase in all 50 states until 2015.
- Kratom is now illegal to buy, sell, or use in Washington, DC; or the states of Wisconsin, Rhode Island, Vermont, Indiana, Arkansas, Alabama, Illinois, and Tennessee (as of June 2018) and other States pending
- Illegal in a few urban counties:

Sarasota, Florida; San Diego, CA; Denver, CO.

- Canadian status is ambiguous.

Curr. Top. Med. Chem. 2011, 11(9):1165-75.

16

16

Early Federal Interest

- In 2001, SAMHSA Office Office of Pharmacologic & Alternative Therapies (OPAT), was contacted by potential importers interested in

"*A new natural cure for opioid addiction from SE Asia!"*

Brief OPAT investigation suggested potential for abuse and unproven but conceivable potential for MAT.

- OPAT Referred to FDA for further action.
- In 2003, DEA included Kratom on their List of Drugs and Chemicals of Concern
- On June 6, 2014, FDA issued an Import Alert (#54-14)
  - 21 U.S.C. 321(ff)(1), 21 U.S.C. 350b(d), 21 U.S.C. 342(f)(1)(B)
- On September 25, 2014, US Marshalls seized >25K lbs in Van Nuys, CA
  - Rosefield Management; raw Kratom material; >$5 million
  - **And the "rush" began…**

Curr. Top. Med. Chem. 2011, 11(9):1165-75.

17

17

01/28/14 AJR-7326315-2 1/1 Kratom Dried Leaves—Net Wt.:21 kgs/case DWH

Product label affixed on the inner bag of the master carton

Picture of product

Close-up of Kratom loose leaves

Batch No. 3 pallet

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In the News

- On September 25, 2014, US Marshalls seized >25,000 lbs of raw kratom material worth more than $5 million from Rosefield Management, Inc in Van Nuys, CA.
- Wholesaler promoted Kratom on its website with **claims that the product is "intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease**." (This claim makes it a drug)
- The FDA filed a complaint in the US District Court of California alleging that kratom is an unapproved new drug and a misbranded drug under the Federal Food, Drug, and Cosmetic Act.
- Meanwhile, back in the lab…

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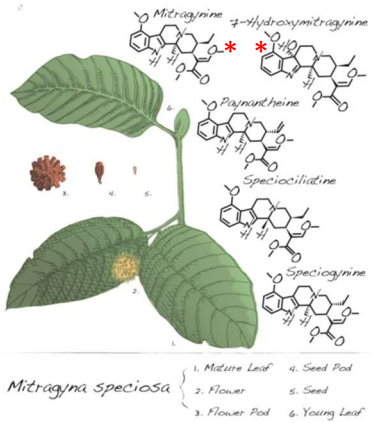

Voucher Specimen

(So we know what plant was actually being assayed)

Kruegel et al. J. Am. Chem. Soc. 2016, 138, 6754–6764
.DOI: 10.1021/jacs.6b00360

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21

Mitragyna Alkaloids

Alkaloid profile of *Mitragyna speciosa* Korth. The percentage is the estimated content in the alkaloid extracts.

Alkaloid	Percentage	Effect	Reference
Mitragynine*	66%	Analgesic, antitussive, antidiarrheal, adrenergic, antimalarial	Hooper (1907); Field (1921); Lee et al. (1967); Ponglux et al. (1994)
Paynantheine	9%	Smooth muscle relaxer	Ponglux et al. (1994)
Speciogynine	7%	Smooth muscle relaxer	Lee et al. (1967); Shellard, 1974; Shellard et al. (1978b); Ponglux et al. (1994)
7-Hydroxymitragynine*	2%	Analgesic, antitussive, antidiarrheal	Ponglux et al. (1994)
Speciociliatine	1%	Weak opioid agonist	Lee et al. (1967); Ponglux et al. (1994)
Mitraphylline	<1%	Vasodilator, antihypertensive, muscle relaxer, diuretic, antiamnesic, immunostimulant, anti-leukemic	Seaton et al. (1958); Shellard, 1974; Shellard et al. (1978b); Ponglux et al. (1994)
Isomitraphylline	<1%	Immunostimulant, anti-leukemic	Seaton et al. (1960); Shellard and Philipson (1966); Ponglux et al. (1994)
Speciophylline	<1%	Anti-leukemic	Shellard and Philipson (1966); Beckett et al. (1966)
Rhynchophylline	<1%	Vasodilator, antihypertensive, calcium channel blocker, antiaggregant, anti-inflammatory, antipyretic, anti-arrhythmic, antithelmintic	Seaton et al. (1960); Shellard, 1974; Shellard et al. (1978b)
Isorhynchophylline	<1%	Immunostimulant	Seaton et al. (1958); Seaton et al. (1960); Shellard, 1974; Shellard et al. (1978b)
Ajmalicine	<1%	Cerebrocirculant, antiaggregant, anti-adrenergic, sedative, anticonvulsant, smooth muscle relaxer	Beckett et al. (1966)
Corynantheidine	<1%	Opioid agonist	Takayama et al. (2002)

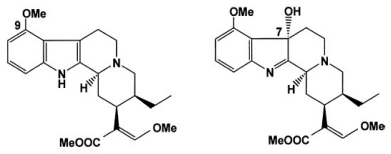
Neurosci. Biobehav. R. 2013, 37:138-51.

22

22

Chemistry

- >40 compounds in *Mitragyna speciosa* leaves
- 2 main opioid alkaloids extracted
  - Mitragynine: 66% by weight
  - 7-hydroxymitragynine: 2% by weight



Curr. Top. Med. Chem. 2011, 11(9):1165-75.

23

23

Structure Activity Relationship Studies

- What's important for opioid activity

Introduction of an OH increases Mu-activity
Acylation of OH decreases activity

Longer alkyl ethers abolish activity
Removal of CH3 decreases activity
Removal of OH creates antagonism
Acetylation decreases activity

N-Oxide abolishes activity

Inversion of stereochemistry abolishes opioid activity

O-replacement with NH abolished activity

Ester hydrolysis or reduction to alcohol reduces activity

Chem. Pharm. Bull. 2004,52(8):916-28.

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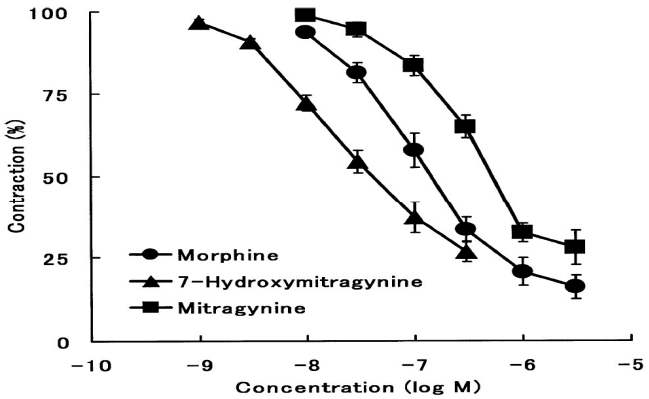
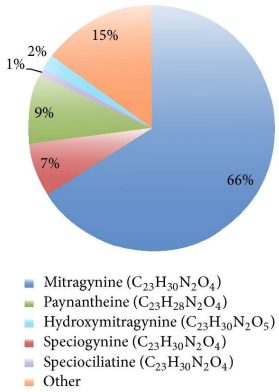


K. Matsumoto et al. / Life Sciences 74 (2004) 2143–2155

25

- Kratom preparations contain varying amounts and proportions of active phytochemicals
- pharmacological and toxicological evaluation highly dependent on preparation and storage
- Mitragynine has a fraction of the Mu agonist potency of Morphine, although a much larger amount of it in the product.
- 7-OH Mitragynine is a Mu opioid receptor agonist and is more than 10 times more potent than morphine (Perhaps 40 times more potent than Mitragynine?)
- **Therefore, most of the opioid activity in the kratom may be coming from that much smaller amount of 7-OH-M**

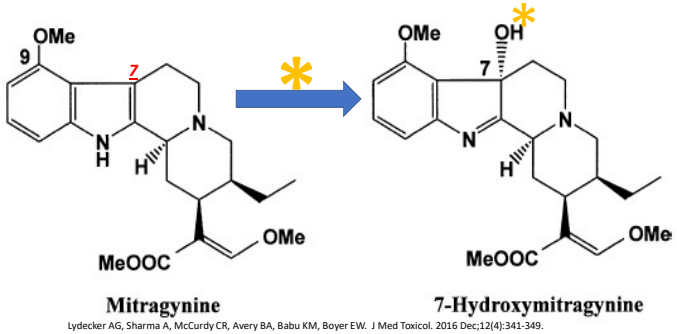


Source: Cinosi E.; Martinotti; et all. Following "the Roots" of Kratom (Mitragyna speciosa): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries; Biomed Res Int. 2015; 2015: 968786

26

Photo-oxidation Chemistry

- **Sunlight may enhance oxidation of Mitragynine to 7-OH-M, so relatively simple conditions of storage or preparation may affect total potency.**
  Higher 7-OH-M concentration may also be a result of "spiking."



Lydecker AG, Sharma A, McCurdy CR, Avery BA, Babu KM, Boyer EW. J Med Toxicol. 2016 Dec;12(4):341-349.

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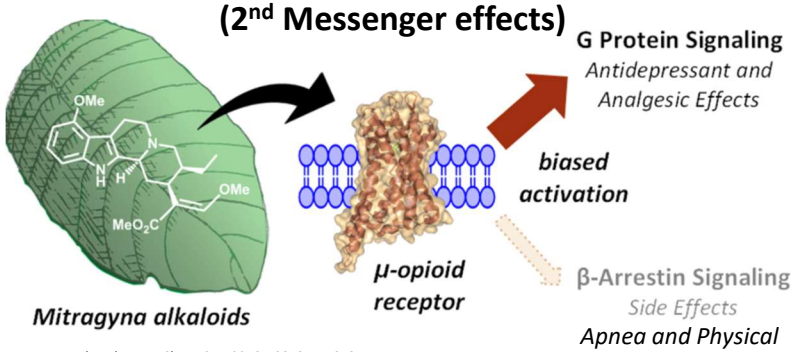
Claim: Biased Signaling at Mu-opioid Receptor (2nd Messenger effects)



Kruegel et al. J. Am. Chem. Soc. 2016, 138, 6754−6764
.DOI: 10.1021/jacs.6b00360

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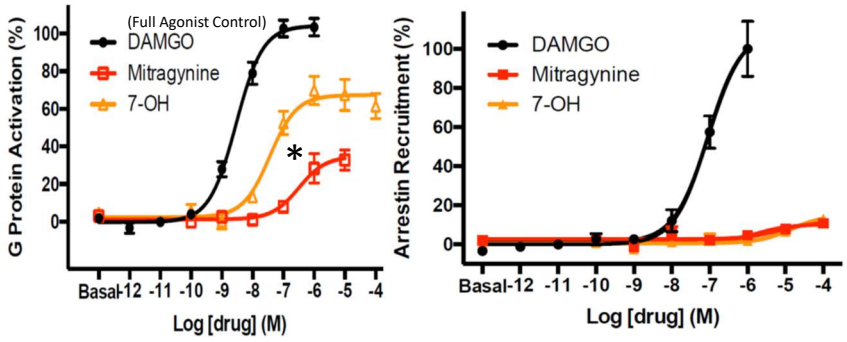

***Partial Agonist Picture (not unlike Buprenorphine?)**

Kruegel et al. J. Am. Chem. Soc. 2016, 138, 6754–6764
.DOI: 10.1021/jacs.6b00360

29

29

Herb-Drug Interactions

- Mitragynine has been reported to inhibit CYP P450:
  - 2C9
  - 2D6
  - 3A4
  - 1A2 (mild inhibition)

Hanapi N. A., Ismail S., Mansor S. M. Inhibitory effect of mitragynine on human cytochrome P450 enzyme activities. Pharmacognosy Research. 2013;5(4):241–246.

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- Kratom has gained popularity for its euphoric effects and is being popularized as a safe herbal product capable of giving a "legal" high (*Swogger et al., 2015*), and as an alternative to other sedative and stimulant type drugs (*Warner et al., 2016*).
- Reports of physical dependence as well as OUD w/kratom in Western nations emerge from case reports from the UK (*Boyer et al., 2008, McWhirter and Morris, 2010*), Germany (*Kapp et al., 2011*) and the US (*Dorman et al., 2014, Nelsen et al., 2010, Forrester, 2013, Sheleg and Collins, 2011*).
- It can be surmised that given the large and growing number of internet purchase sites for kratom (cited in *Cinosi et al., 2015*), addiction to kratom is also likely to be growing in Western countries.
- No treatment specific for kratom addiction is available, however, as an Opioid Use Disorder (OUD), either medication assisted treatment (MAT) or opioid detoxification might be reasonable.
- Two cases of NAS reported in infant whose mother was a kratom user and who responded to opioid treatment.

31

31

Neonatal Abstinence Syndrome

- Report of baby delivered to user of 18-20g / day for 2 years requiring NICU admission on postpartum day 2 (feeding intolerance, jitteriness, irritability and vomiting) with morphine taper over 5 days.

- Another report of a term neonate born to a chronic Kratom user and required treatment with opioids for successful neonatal drug withdrawal.

Mackay, Lindsay, and Ronald Abrahams. Novel case of maternal and neonatal kratom dependence and withdrawal. Canadian Family Physician 64, no. 2 (2018): 121-122.
Davidson L., Rawat M., et al. Natural drugs, not so natural effects: Neonatal abstinence syndrome secondary to 'kratom'. J Neonatal Perinatal Med. 2018 Aug 22.
Smid, M. C., Charles, J. E., Gordon, A. J., & Wright, T. E. (2018). Use of kratom, an opioid-like traditional herb, in pregnancy. Obstetrics & Gynecology, 132(4), 926-928.

32

32

Market Availability

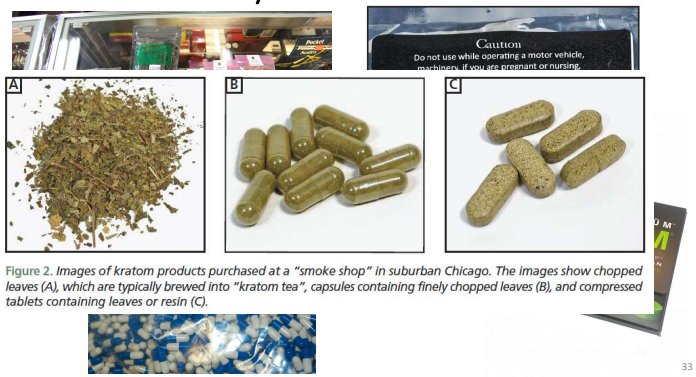

Figure 2. *Images of kratom products purchased at a "smoke shop" in suburban Chicago. The images show chopped leaves (A), which are typically brewed into "kratom tea", capsules containing finely chopped leaves (B), and compressed tablets containing leaves or resin (C).*

33

33

- Kratom Definition 15 oz Ceramic Large Mug Kratom Definition Mugs by

Support Kratom - CafePress

34

Current Legal Status

- Currently uncontrolled under federal regulation

- In August 2016, DEA submitted a notice of intent to temporarily schedule the opioids mitragynine and 7- hydroxymitragynine, as schedule I substances under the CSA

- American Kratom Association, a self-described nonprofit consumer advocacy organization claims to represent 5 million Kratom users in the US successfully campaigned for withdrawal of planned scheduling, including submission of petition to White House

- DEA withdrew scheduling request in October 2016

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- An anonymous online survey was conducted in October 2016 of 10,000 current kratom users through available social media and from the American Kratom Association (https://speciosa.org/home/)
- 8,049 respondents completed the survey.
- Findings:
  - Kratom was primarily used by a middle-aged (31-50 years) males (56.91%) with income $35,000 or higher with private insurance (61.31%).
  - Kratom was used to self-treat pain (68%) and emotional or mental conditions (66%) and for withdrawal symptoms associated with prescription opioid use.
  - Subjects reported dose-dependent nausea and constipation with high doses (5g) and with and frequent dosing (Q22 doses/wk).

SOURCE: Grundmann O.; Patterns of kratom use and health impact in the USVresults from an online survey. Drug Alcohol Depend. 2017; 175(5):63Y70.

36

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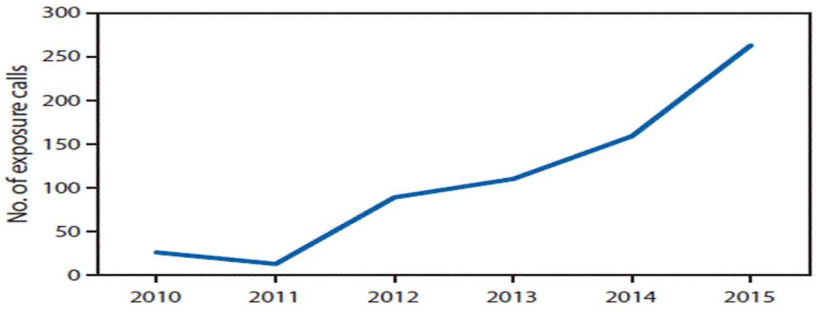
National Poison Data System - United States (includes Puerto Rico)
January 2010–December 2015



SOURCE: Anwar M, Law R, Schier J. Notes from the Field. Kratom (Mitragyna speciosa) Exposures Reported to Poison Centers — United States, 2010–2015. MMWR Morb Mortal Wkly Rep 2016;65:748–749. DOI: http://dx.doi.org/10.15585/mmwr.mm6529a4

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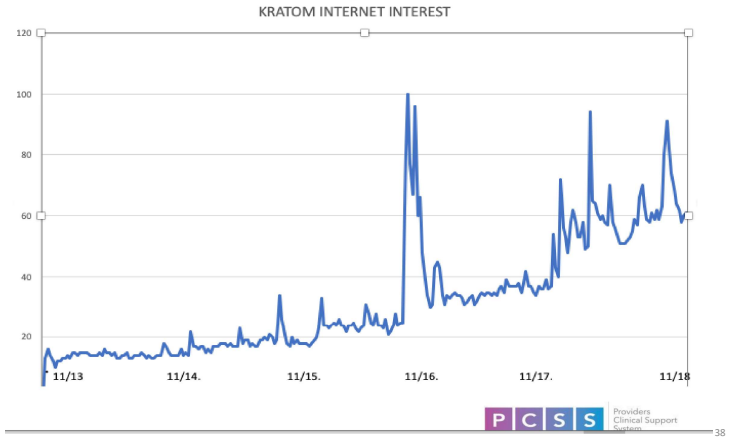

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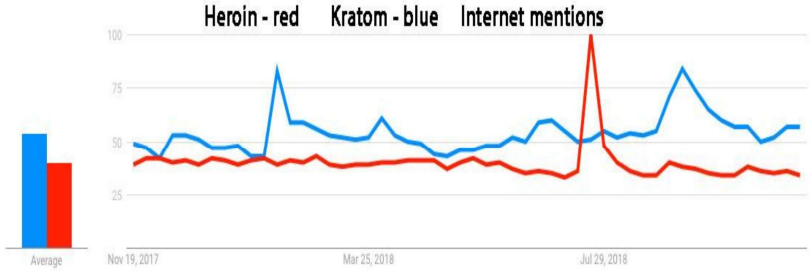

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From July 2016 to June 2017, 25 fatal overdoses involving kratom across 8 CDC SUDORS states were identified

States	ME	NH	NM	OH	PA	RI	WV	WI	Total
Opioid overdose deaths	301	402	322	4,534	3,231	265	844	825	10,724
Deaths involving kratom	4	2	1	3	8	1	5	1	25
Percent involving kratom	1.3%	0.5%	0.3%	0.07%	0.25%	0.4%	0.6%	0.1%	0.23%

Caution: testing of kratom is not uniform thus these numbers are underestimates

Source: CDC SUDORS Overdose Death Data

In 2017, the Food and Drug Administration (FDA) began issuing a series of warnings about kratom and has now identified at least 44 deaths related to its use.

Kratom associated illness has been reported with either microbial contamination or heavy metal adulteration.

Most kratom associated deaths appeared to have resulted from adulterated products or taking kratom along with other potent substances.

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Kratom is now restricted or illegal in:

Australia	Lithuania	Romania
Denmark	Myanmar	South Korea
Finland	Malaysia	Sweden
Israel	Poland	Thailand
United Kingdom		

Scheduling under consideration in U.S.

On November 14, 2017, the FDA issued a public health advisory related to mounting concerns regarding the risks associated with kratom and reported deaths with use.

Wake up and smell the Coffee?

41

41

One View

- Although the available data may show a lack of power and systematic approach, available evidence points towards potential for use and/or abuse of mitragynine, hydroxymitragynine and derivative preparations.
- Preliminary analysis points towards mitragynine meeting some the necessary criteria for placing a substance into Schedule I of the CSA under 21 U.S.C. 812(b)(1), such as:
  - The drug or other substance has a high potential for abuse
  - The drug or other substance has no currently accepted medical use in treatment in the United States
  - There is a lack of accepted safety for use of the drug or other substance under medical supervision

42

42

On the Other Hand

- Animal data and human experience point toward pharmacologic activity, including Mu opioid potential.
- While few deaths have been reported for Kratom alone as a Cause of Death (COD), they do occur. Kratom is also found as a contributor in many poly-drug overdoses, as are all prescription opioids.
- There are theoretical reasons, with some support data, that kratom derivatives might offer a safer profile than current standard full agonist opioids.
  - Partial agonist (like buprenorphine)
  - "Biased" agonism, (less B-Arrestin / G-Protein activation)
- In the context of unmet need for new options in both pain management and Medication Assisted Treatment (MAT), a safer opioid with such a profile might be useful or beneficial.
- **For Kratom-related products to be used medically or marketed safely, regulation or some other form of social control would be required to assure product consistency, quality and microbial safety. Controlling abuse of mitragynine, hydroxymitragynine and related plant preparations will remain a thorny issue**.

43

43

Summary

- Evidence suggests that Kratom is being used extensively for both medical and non-medical purposes
- Mitragynine and derivatives might potentially be used for management of pain, opioid withdrawal symptoms, and other clinical problems.
- Questions remain regarding the potential toxic effects and abuse and addiction potential of Kratom.
- Possibilities of Kratom products being adulterated or interacting with other drugs are a serious concern.

44

44

- Kratom is a recognized emerging public health threat (*MMWR. July 29, 2016;65(29):748Y749)*
- People need to understand that ‘‘legal’’ and ‘‘available’’ are not the same as ‘‘safe.’’
- In the West, kratom is becoming valued for analgesic effects and to aid in managing opioid withdrawal. However, some of these individual attempts have resulted in cases of toxicity and fatalities.
- Physicians should be aware of these herbal supplements and potential toxicity or withdrawal effects in patients including in newborns which cannot be picked up by the standard toxicology screen (*Davidson et al, 2018*).
- Preventionists should be aware of this drug and work with their communities raising awareness, providing education about effects and risks.

45

45

Washington Post: In a first, FDA orders recall of a ‘contaminated food’ — kratom with salmonella (April 3, 2018)

Archived Files

Archived Kratom Information

(HTTPS://NDEWS.UMD.EDU/RESOURCES/KRATOM)

NDEWS National Drug Early Warning System

Funded at the Center for Substance Abuse Research by the National Institute on Drug Abuse

Fact Sheets

Drug Enforcement Administration Fact Sheet

Drug Enforcement Administration: Mitragynine and 7-hydroxymitragynine

NIDA: DrugFacts: Kratom

EMCDDA Fact Sheet

Journal Articles

Traditional and Non-Traditional Uses of Mitragynine (Kratom): A Survey of the Literature

A Case Report of Kratom Addiction and Withdrawal

Pharmacology of Kratom: An Emerging Botanical Agent with Stimulant, Analgesic and Opioid-Like Effects

Self-Treatment of Opioid Withdrawal Using Kratom

MMWR *Notes from the Field*: Unintentional Drug Overdose Deaths with Kratom Detected — 27 States, July 2016–December 2017

Notes from the Field: Kratom (Mitragyna speciosa) Exposures Reported to Poison Centers-- United States, 2010-2015

Senate Passes Bill Regulating Sale of Kratom

Kratom: Natural Painkiller or Addictive Drug

Kratom, an Addict's Alternative, is Found to Be Addictive Itself

46

46

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47

47

48