

Kratom

TOR Webinar 7.28.21 Eric Martin



- Kratom is a tropical tree, *Mitragyna Speciose*, native to Southeast Asia (Thailand, Malaysia & Indonesia). Consumption of its leaves produces both stimulant effects (in low doses) and sedative effects (in high doses), and can lead to psychotic symptoms, and dependence.
- Kratom leaves contain two major psychoactive ingredients (mitragynine and 7-hydroxymitragynine). These leaves are crushed and then smoked, brewed with tea, or placed into gel capsules. Kratom has a long history of use in Southeast Asia, where it is commonly known as thang, kakuam, thom, ketum, and biak. Used as a traditional medicine for pain.



(DEA & SAMSHA)

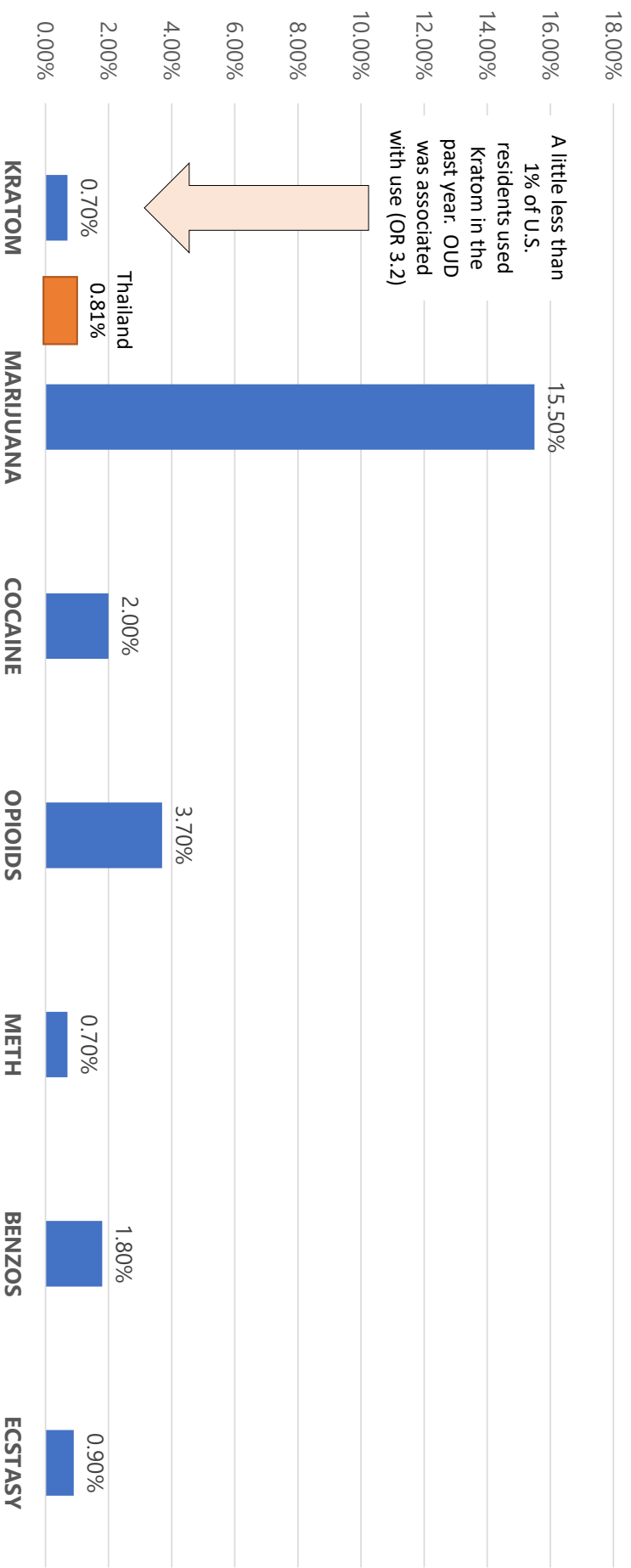


Kratom: How Used

- Capsules, tablets
- Extract
- Leaves
- Chewed
- Brewed as tea
- Smoked



Kratom Prevalence



- *American Journal of Preventive Medicine* (2021), Past Year Kratom Use in the U.S.: Estimates from a Nationally Representative Sample
- NSDUH National Survey on Drug Use and Health (2019)

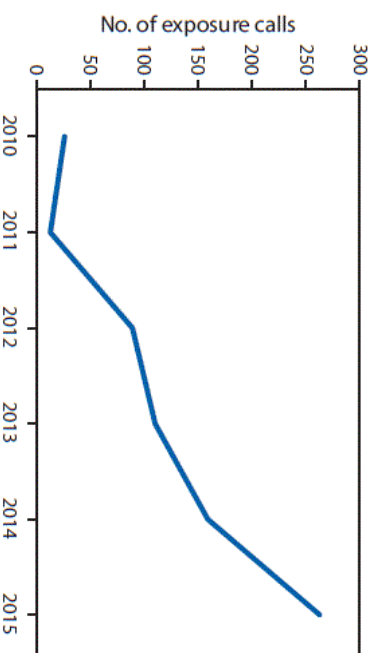
SUMMARY POINTS

Less than 1% of U.S. residents used Kratom in the past year, and most of them had Opioid Use Disorder with Rx Pills. Despite few U.S. residents using Kratom, it is sold in convenience stores, head shops, porn stores, and Kratom Bars in several states.

Kratom: Poison Control

Poison control centers in the United States received about 1,807 reports involving use of kratom from 2011 through 2017, including deaths. About half of these exposures resulted in serious negative outcomes such as seizures and high blood pressure. Five of the seven infants who were reported to have been exposed to kratom went through withdrawal.

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.



- 2016-17: Analyzing 27,338 overdose deaths, 152 involved Kratom, usually in combination with other drugs.
- Of 152 deaths, 91 were determined to be Kratom deaths, of which 7 was the only drug.

SE ASIA: Kratom, Cough Syrup & Coke

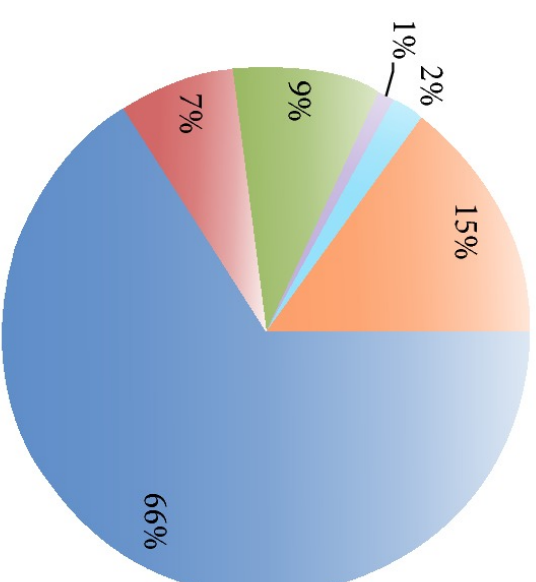


SUMMARY POINTS

In the U.S. Kratom users are typically addicted to Rx Opioid pills, and most overdose deaths involving Kratom usually involve other drugs. We don't know if people in the U.S. are mixing Kratom with cough syrup and coke.

Kratom Extract Composition

- Kratom preparations contain varying amounts of several phytochemicals, making their pharmacological and toxicological evaluation unique and difficult.
- More than 40 alkaloids in kratom have been identified in the laboratory.
- The two major psychoactive alkaloids are Mitragynine and 7-hydroxymitragynine.
- Mitragynine makes up to 66% of Kratom's alkaloids.
 - Partial mu-receptor & kappa agonist
 - Half-life: 3.5 hours
- 7-hydroxymitragynine makes up 2%.
 - Mu & Kappa receptor agonist
 - Half-life: 2.5 hours
- Kratom inhibits CYP 3A4, 2D6, 1A2 liver enzymes creating a significant potential for drug interactions.



- Mitragynine ($C_{23}H_{30}N_2O_4$)
- Paynantheine ($C_{23}H_{28}N_2O_4$)
- Hydroxymitragynine ($C_{23}H_{30}N_2O_5$)
- Speciochloratene ($C_{23}H_{30}N_2O_4$)
- Other

Source: Cinosi E.; Martinotti; et al. 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
University of Utah Health, 2017, presentation, Paula Cook, MD & Mikayla Mills, Pharm.D.

Red vs. White or Green



Red Vein

Allegedly contains a higher proportion of 7-hydroxymitragynine.



Green Vein



White Vein

Allegedly contains a higher proportion of mitragynine.

Relaxing



Stimulating

Kratom: Effects

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.

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

Babu, Kavita M.; McCurdy, Christopher R.; Boyer, Edward W. (2008). "Opioid receptors and legal highs: Salvia divinorum and Kratom". *Clinical Toxicology*. 46 (2): 146–152. 149.



SUMMARY POINTS

Mitragynine and 7-hydroxymitragynine are Kappa-receptor agonists and partial Mu-receptor agonists

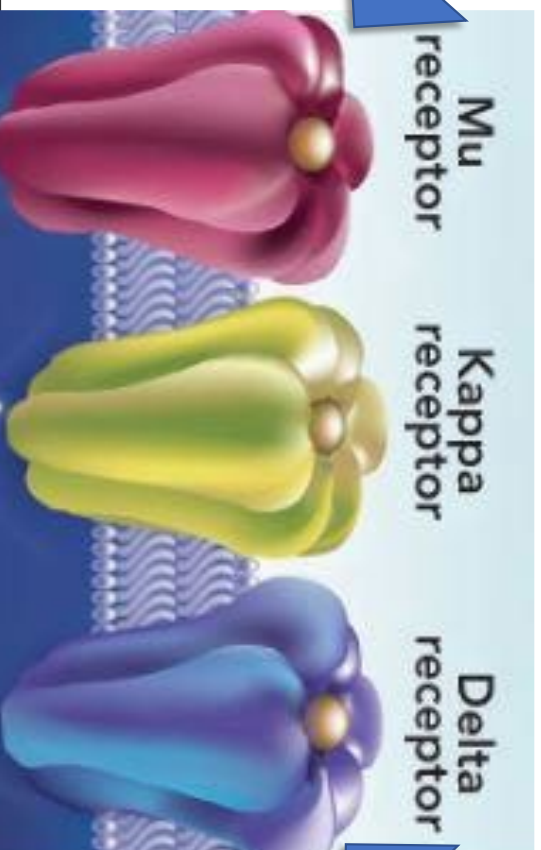
Partial activation



Full activation

Partial activation

Pain relief
A lot of euphoria



Full activation

Pain relief
Minimal euphoria
Psychological effects

Kratom side effects

Kratom has a number of known side effects, including:

- Weight loss
- Dry mouth
- Chills, nausea and vomiting
- Changes in urine and constipation
- Liver damage
- Muscle pain

Kratom also affects the mind and nervous system:

- Dizziness
- Drowsiness
- Hallucinations and delusion
- Depression and delusion
- Breathing suppression
- Seizure, coma and death

KAPPA receptor drugs

Kappa-receptor agonist research:

- Kappa agonists are analgesic
- Kappa agonists lack side effects of Mu agonists (constipation & respiratory depression), lower addiction liability.
- In mice studies Kappa agonist reduce the compulsion to use cocaine & opioids, possibly an addiction treatment drug.

SUMMARY POINTS

While Kappa agonists are “promising” drugs to help medicate pain, have lower addiction potential, and lower risk for fatal overdose, and possibly treat addiction to cocaine & other opiates, Kratom is likely not one of these promising drugs.

- Kratom activates both Mu & Kappa receptors.
- Kratom can induce dependence.
- Kratom has other side effects that make it less than ideal.

Use of Kratom in the US

- 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, 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.

SOURCE: Grundmann O.; Patterns of kratom use and health impact in the USVresults from an online survey. Drug Alcohol Depend. 2017; 175(5):63V70.

Dosage

- Low-doses (1-5 grams) have stimulating effects.
- Higher-doses (5-15 grams) have opioid-like effects.

Kratom Concerns

- 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 on 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 the Western countries.
- Withdrawal symptoms (University of Utah Health, 2017):
 - Muscle/bone aches
 - Insomnia
 - Irritability
 - Aggression
 - Runny nose

Kratom Treatment

- No studies have evaluated Treatment Best Practices for “Kratom Use Disorder”.
- Case studies reveal success treating Kratom dependence with Buprenorphine.
- Use Naloxone for Kratom overdose

Kratom Legal Status

- DEA filed to have Kratom scheduled as Schedule I
- Withdrew application in 2016 due to public protest
- 51 representatives and 9 senators responded to the application under pressure from their constituents
- Various states have attempted to pass legislation to control or restrict use.

Prohibited:	Legal for Adults:	Legal:
Alabama	Illinois	All other states
Arkansas	New Hampshire	
Indiana		
Rhode Island		
Vermont		
Wisconsin		

