Kratom:
An Emerging Issue and Need for Regulations in the United States

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ABSTRACT

Objective: To understand and highlight the current issues, emerging trends, and regulations of kratom in the United States.

Data Sources: PubMed and PubMed Central of the National Library of Medicine, MEDLINE, PsycINFO, and ClinicalTrials.gov databases were utilized.

Study Selection: Studies published between January 1, 2000, and June 30, 2020, were accessed by using the MeSH term *mitragyna* in the context of *toxicity*, *safety*, and *legislation and jurisprudence*.

Data Extraction: The final qualitative synthesis included 11 studies by following Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement guidelines.

Results: The US Drug Enforcement Administration (DEA) initially proposed to place kratom under Schedule I of the Controlled Substances Act, but the DEA later withdrew the intent, and kratom is still a legal substance in most of the United States. A low to moderate kratom dose produces mild stimulant properties, whereas large doses produce sedative effects that are identical to opiates. Its regular use at a higher dose is associated with dependence. Management of overdose is similar to that of patients presenting with opioid abuse, although kratom may potentially pose a higher risk for drug toxicity and organ injury compared to opioids due to intrinsic properties and adulteration. There is no clinical evidence for its safety and efficacy. The US Food and Drug Administration and the DEA do not recognize any legitimate medical use of kratom.

Conclusions: Kratom is an emerging public health concern and is abused as an alternative to opioids. Stringent policies and public awareness campaigns are required to curb the perception of its safe use, which needs to be substantiated with well-designed clinical trials.

Prim Care Companion CNS Disord 2021;23(1):20r02770

To cite: Shah K, Tankersley W, Mekala H. Kratom: an emerging issue and need for regulations in the United States. *Prim Care Companion CNS Disord*. 2021;23(1):20r02770.

To share: https://doi.org/10.4088/PCC.20r02770

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Over the years, humans have been engaging in the consumption of substances that are not necessary for survival but are capable of changing the body's physiologic parameters, perception, and behavior through their psychoactive properties.[1] These compounds, which occur naturally in plants in particular regions of the world and are often known for their local use, are now being highlighted in the global market due to the constant search for new psychoactive drugs.[2] While these substances in their original forms are not frequently associated with addiction, they may have strong addiction potential as purified substances.[3]

Mitrgyna speciosa (*M. Speciosa*) of the *Rubiaceae* (coffee) family, which grows primarily in the tropical and subtropical regions of Southeast Asia and Africa, is an example of such a plant that has psychoactive potential. It is known by different names such as biak-biak or ketum in Malaysia and kratom, kakuam, kraton, or ithang in Thailand.[4,5] Traditionally, leaves of this plant are used to treat cough, diarrhea, muscle pains, and intestinal infection.[5] Literature[6] has shown that the potential use of these plant leaves has changed from local remedy purposes to that of opioid use, associating it with abuse potential. Even though several European countries have banned the plant due to its active alkaloids and abuse potential, an increase in kratom sales trends and its use was observed in Europe and North America, raising concerns about public safety.[7]

EPIDEMIOLOGY

The prevalence of kratom use is steadily rising in the United States.[8–11] The estimated number of users in the United States is about 3 to 5 million, which corresponds to 0.9%–1.5% of the total US population.[12] As per the National Poison Data System, the increase in kratom consumption was seen from the year 2000.[8] Due to the widespread consumption of kratom, its monthly import to the United States is estimated at about 2,000 metric tons.[9] The first kava bar that served kratom opened in Florida in 2002.[9] While kratom has been available in the United States for at least 10 years, poison control centers reported a significant increase in kratom-related overdose between 2011 and 2015.[13] Of these overdoses, the Centers for Disease Control and Prevention (CDC) classified 49 (7.4%) of 660 cases as life threatening with some residual disability.[14]

In 2017, the US Food and Drug Administration (FDA) identified 44 deaths related to kratom.[14] Data from 2011 to 2017 of the National Poison Data System found 11 deaths associated with kratom exposure, of which 9 cases were determined to have simultaneous involvement of other illicit drugs, alcohol, caffeine, fentanyl, or benzodiazepines.[14] As per the CDC, about 25 deaths were associated with kratom use between July 2016 and June 2017 and were considered to be due to its concomitant use with other potent substances or adulterated products.[15]

Clinical Points

- Current evidence has not yet established the role of kratom in pain management and opioid withdrawal symptoms in humans.
- Well-designed clinical human studies are needed to determine kratom's safety and efficacy and to better understand various aspects of its clinical application, including dosing, frequency, and route of administration.
- Risk of overdose, toxicity, and life-threatening adverse events due to kratom use is high due to its easy availability and unregulated production standards.

Kratom is primarily used to treat chronic pain and mood disorders and mitigate the withdrawal symptoms of a prescription or illicit drug.[12] An online survey[12] conducted in 2016 revealed that middle-aged (31–50 years) men (56.91%) with private insurance (61.31%) and income > $35,000 were primarily involved in kratom use. About 68% of the survey respondents reported its use to treat pain and 66% for emotional or mental conditions and withdrawal symptoms associated with prescription opioid use.[12]

Another anonymous survey[7] on kratom use revealed that of 500 respondents, 20.8% admitted to lifetime use and 10.2% reported usage in the past 12 months. Users of kratom were younger (31.1 vs 35.9 years, respectively) and more versatile substance users compared to other substance users. A majority (68.9%) admitted using the drug as a means of reduction or abstinence from nonprescription opioids or heroin, whereas 64% used kratom as a substitute for nonprescription opioids or heroin.[7]

It remains relatively easy to purchase kratom in the United States through head shops, kava bars, and the internet. Kratom's popularity is on the rise because it is considered a legal, psychoactive alternative to other sedatives and stimulant-type drugs.[17–19] In 2019, the Substance Abuse and Mental Health Services Administration raised concerns regarding kratom, and its use was labeled an emerging issue along with marijuana and e-cigarettes.[20]

Evidence from various studies[13,19,20] also proved that the plant possesses both stimulant and dose-dependent effects, with mitragynine and 7-hydroxy mitragynine (7-HMG) as its primary alkaloids. While a few states have legislation against its use, kratom mostly remains a legal substance in the larger part of the United States and the world.[7,14] However, there is currently no clinical evidence for its safety and efficacy.[15] Kratom is an emerging public health threat due to easy accessibility, reported adulteration, toxicity, adverse events, deaths, unawareness of the risks associated with use, addictive properties, and safety perception.[7,17] In this article, the objective is to address the existing challenges and barriers with regard to kratom, including forms of use, pharmacology and toxicity, clinical safety and efficacy, abuse and dependency, comparison with opiates, and management of overdose and withdrawal. The article also highlights and contributes to the understanding of current issues, emerging trends, and regulations pertaining to kratom in the United States.

METHODS

A literature search was conducted using the MEDLINE database for articles published between January 1, 2000, and June 30, 2020, for the MeSH term *mitragyna* in the context of *toxicity*, *safety*, and *legislation and jurisprudence*. A similar strategy was adapted to search additional literature in databases including PubMed and PubMed Central of the National Library of Medicine, PsycINFO, and ClinicalTrials.gov. Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines[21] were followed to screen relevant articles by identifying the key terms *toxicity*, *safety*, *efficacy*, and *regulations*. The titles and abstracts were screened on the basis of the purpose of our study objective, and 18 duplicate records were excluded. After reviewing the full text further, we included 11 studies[7,8,12,13,22–28] for the systematic review as shown in Figure 1.

RESULTS

Kratom: Overview

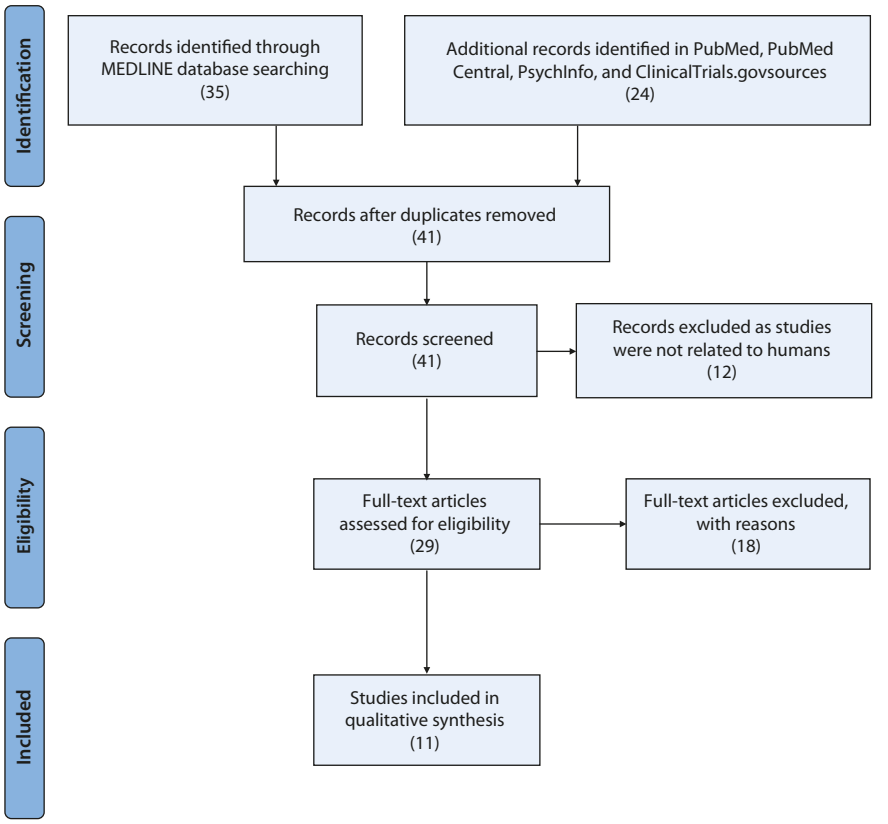
The use of kratom has increased worldwide due to its stimulating effects and utilization as an opioid substitute. It is associated with psychosis, seizures, intrahepatic cholestasis, and death. Research data suggest that apart from stimulant and sedative dose-dependent effects, kratom also has antinociceptive effects, antidepressant activity, anxiolytic-like effects, and anorectic effects.[4] The drug's effects and safety of use have led to a growing concern due to the increase in hospital visits and deaths.[18,29] To control the use of kratom in Florida, the state has introduced a bill to ban its use, but kratom still remains legal except in Sarasota County.[19,20,22] According to the International Narcotics Control Board of the United States, between February 2014 and July 2016, the agencies encountered 55 tons of kratom, equating to 50 million doses.[30]

According to the American Association of Poison Control Centers, a 10-fold increase was seen in kratom use from 2010 (N = 26) to 2015 (N = 263). Of 660 reported calls to poison centers, about two-thirds were from health care providers.[29,31] About 65% of the calls reported isolated use of kratom, males accounted for 75% of users, and about 7% were classified as major and life threatening.[29,31] Cases included 487 (73.8%) intentional exposures, 595 (90.2%) drug ingestions, and 428 (64.8%) isolated kratom exposures.[18,29,31]

Available Products, Usage Methods, and Purposes

M. Speciosa products are now widely available on the internet, and they can be used either recreationally or therapeutically. Different forms available for consumption include resins, dried leaves, capsules, pills, extracts, and powder.[10,16,32,33] For recreational purposes, leaves can be chewed, brewed as tea, or smoked.[16] Powdered kratom

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram of the Study



products are advertised in 2 to 6 g and can be consumed by mixing with water, juice, milk, tea, hot chocolate, or smoothie.[34–39]

Therapeutically, leaves are traditionally used in Malaysia and Thailand to treat cough, diarrhea, muscle pains, and intestinal infection.[38] Reports of its use to alleviate opioid withdrawal symptoms from heroin or morphine dependence were also documented.[40]

Mechanism of Action

More than 25 alkaloids were found in kratom leaves, with primary ones being mitragynine and 7-HMG.[40] Mitragynine was found to have approximately 13 times more potency than morphine and is considered to be a main chemical compound in kratom. Current research reveals that 7-HMG has antidepressant effects and is a 4 times more potent central nervous system stimulant than mitragynine.[32]

The effects of kratom are complex and may provide either stimulant or opioid-like effects.[27] Relative levels of stimulation or mood enhancement and sedative or analgesic effects depend on the strain of kratom chosen and quantity ingested, with the white vein strain providing more energy and stimulating effects than the green vein variety.[34] The full effects of kratom after consumption are usually observed in about 30 to 60 minutes, with peak effects at 2 to 4 hours and lasting approximately 5 to 7 hours.[34]

Pharmacology

Considering the diversity of alkaloids present in kratom extracts, and its unique pharmacodynamic properties, the physiologic effects it can produce are complex.[6] Both mitragynine and 7-HMG target opioid receptors, though they have significant differences in binding affinity. Mitragynine was found to have less affinity than morphine, whereas 7-HMG is 46 times and 13 times more potent than mitragynine and morphine, respectively.[27] This increased potency of 7-HMG alkaloid of mitragynine is due to the additional hydroxyl group on 7-HMG.[10]

Mitragynine exhibits activity on supraspinal μ and β opioid receptors, causing its characteristic analgesic effects.[41] Studies proved that at the cellular level, the neurotransmitter released from the nerve endings at the vas deferens is inhibited due to the blockage of neuronal calcium (Ca2+) channels.[28] On the other hand, blocked stimulation of postsynaptic α_2-adrenergic receptors contributes to the stimulant activity.[28,40]

Metabolism in humans is through different mechanisms such as hydrolysis, demethylation, oxidative and reductive transformations, and glucuronide and sulfate conjugate formation in phase I and phase II.[32] Kratom was also found to have a potential drug interaction with cytochrome P450 (CYP) enzyme activity.[42] CYP1, CYP2, and CYP3 are the subfamilies of CYP and are responsible for the metabolism of >90% of commercially available drugs.[43] It was found that *M.*

Speciosa extract exhibits competitive inhibition of CYP2D6 and noncompetitive inhibition for CYP1A2, CYP2C19, and CYP3A4, raising concern for drug interaction if concomitant medications are metabolized through the same enzymes.[42]

Toxicology: Related Adverse Events and Death in the United States

Regular use of kratom may not constitute to dependence or addiction. However, the risks associated with kratom occur due to altering the composition and increasing its potency, which further leads to toxicity.[44] Kratom is often used in combination with other illicit drugs as well as prescription drugs such as opioids, benzodiazepines, and antidiarrheal medications such as loperamide, leading to serious side effects.[42,43,45]

Evidence from a few case reports showed that patients developed aspiration pneumonia, fever, and seizure following consumption of kratom.[36,37] Other clinical presentations identified by the National Poison Data System[8] include agitation (18%), confusion (8.1%), drowsiness (13.6%), hallucinations (4.8%), seizures (6.1%), and tachycardia (16.9%) that eventually progressed to cardiac arrest (0.6%) and coma. Death was also reported in Florida in 2014 due to kratom use.[20] It was also reported that the addition of substances such as phenylethylamine or O-desmethyl tramadol have resulted in patient deaths.[46] However, the cases were due either to long-term consumption or an acute overdose. As per the online survey conducted by the American Kratom Association in October 2016, dose-dependent nausea and constipation associated with high doses (5 g) and toxicity occurred when doses exceeded 8 g.[6,12,25]

Safety and Efficacy of Kratom

There is no clinical proof yet for the safety and efficacy of kratom in the United States, and the US Drug Enforcement Administration (DEA) December 2010 version of the Drugs and Chemicals of Concern list states that there is no legitimate medical use of kratom in the United States.[46] As per ClinicalTrials.gov, 2 research studies are registered and recruiting subjects, first to assess the pharmacokinetics and drug interaction liability of kratom and second to evaluate potential analgesic properties of kratom using the cold pressor task.[47]

Abuse and Dependency Among US Adults and Adolescents

Consumption in small doses has been shown to produce effects similar to stimulants such as cocaine and amphetamines. Large doses produce sedative effects that are identical to opiates.[16] Regular use of kratom, especially at higher doses, is associated with dependence, tolerance, and withdrawal.[6,16] However, reports suggest that abstaining from kratom is typically associated with milder symptomatology than abstinence from classical opioids.[6] It was also concluded that kratom has both less liability and a much lower risk of fatal overdose than traditional opioids.[47]

Comparison With Opiate Drugs

On February 6, 2018, the FDA declared kratom as a dangerous drug with opioid properties.[7] However, mitragynine, the alkaloid responsible for its pharmacologic effects, has been shown to interact directly with other CNS drug targets, rendering it distinct from traditional opioids.[48] Evidence has proved that kratom's effects differ from those of classical opioids.[6] For instance, a low to moderate dose of kratom produces mild stimulant properties, whereas conventional opioids have a sedating effect; furthermore, kratom does not seem to create an intense high or euphoria at typical doses and is less likely to cause respiratory depression unlike opioids.[6,29,49]

Opiate Abusers Switching Due to Strict Opiate Laws

More than 47,000 Americans died in 2017 as a result of an overdose on opioids; in the same year, an estimated 1.7 million people suffered from disorders relating to prescription opioid pain disorders.[50] Overdoses on opioids increased by 54% from 2016 to 2017 in metropolitan counties of 16 states.[51] These overdoses have led to a declaration of an opioid crisis and stricter laws concerning prescription and consumption of opioids. However, it is unclear if the increasing trend in kratom use is due to the strict opiate laws. Growing trends of kratom use are also attributed to its legal status in most regions.[52,53]

Current Dosing and Units

Due to the lack of data from clinical trials, the authentic information regarding dosing and units of various forms of kratom is unavailable. However, dosing information was found based on our research and is shown in Table 1.[53]

Powdered kratom products are commercially available in the United States in recommended doses of 2 to 6 g. However, it largely depends on the mitragyna strain used, as users mostly titrate themselves beginning with lower doses until the desired effect is reached.[54]

Detox and Management of Overdose and Withdrawal

According to the American Addiction Centers, management of abuse and withdrawal has 3 phases: (1) physical stabilization, (2) therapy, and (3) recovery. Symptoms of withdrawal include complaints such as nausea, vomiting, chills, diarrhea, body aches, restlessness, and irritability.[54] Evidence suggests that a combined therapy of buprenorphine and naloxone can alleviate both the physical and mental symptoms.[55]

It takes about 5 to 7 days to detox kratom. Factors such as length of use, amount, and dependency influence the length of detox and the intensity of withdrawal.[56] To treat kratom dependence, antidepressants, anxiolytic drugs, anti-inflammatory medications, and other pharmacologic agents have been found to be useful.[57]

Management of overdose is similar to that of patients presenting with opioid abuse, though kratom may potentially pose a higher risk for drug toxicity and organ injury compared to opioids due to intrinsic properties and adulteration.[51]

Regulations

In August 2016, the DEA initially intended to place the active alkaloids of kratom, mitragynine, and 7-HMG under Schedule I of the Controlled Substances Act to restrict its use, but the proposal was later withdrawn.[10] Currently, the DEA has listed kratom as a drug and chemical of concern.[58]

The FDA issued a warning not to use kratom, did not approve it for medical use, and placed it on the list of unapproved drugs.[16,59] Following this alert in 2012 and a second alert in February 2014, the FDA took the following additional actions:

- In September 2014, US Marshals, at the FDA's request, seized more than 25,000 lb of raw kratom material worth more than $5 million from Rosefield Management, Inc in Van Nuys, California.[59]
- In January 2016, US Marshals, at the FDA's request, seized nearly 90,000 bottles of dietary supplements labeled containing kratom and worth more than $400,000.[59]
- In August 2016, US Marshals, at the FDA's request, seized more than 100 cases of products labeled containing kratom and worth more than $150,000.[59]

Concerns about legality are due to its potential therapeutic value as a substitute for opioids on the one hand, and the dangerous and addictive potential on the other.[2,8,60,61] In the United States, kratom remains legal, except in Alabama, Arkansas, Indiana, Vermont, and Wisconsin.[51,62,63] In 2020, the Oklahoma House of Representatives passed a kratom Consumer Protection Act with an anonymous vote of 97–0, which requires vendors to label products with dosing

Table 1. Summary of Kratom Dosing and Units in Available Forms[55]

Forms of Kratom	Dose	Unit
Average powdered leaf	1 g 50 g 100 g	0.035 oz 1.75 oz 3.5 oz
Crushed leaf	1 tablespoon 1 teaspoon	2.5 g 0.9 g
Bali powder	1 tablespoon 1 teaspoon	6.2 g 2.35 g
Maeng Da powder	1 tablespoon 1 teaspoon	7 g 2.6 g
Green Malay	1 tablespoon 1 teaspoon	6.9 g 2.4 g

Table 2. Summary of Studies Included for Qualitative Synthesis

Source	Study Objective	Conclusion
Veltri and Grundmann, 2019[7]	Provide impact of kratom use on consumers with current perspectives	Kratom is unscheduled as per the US Controlled Substances Act, although the US Drug Enforcement Administration has not recognized its legitimate use for medicinal purposes. This study has also found variable legal regulations across states. Due to the potential risk of side effects, drug-to-drug interaction, dependency, and toxicity, appropriate labeling of kratom products and creating awareness among clinicians for the benefit of their patients was emphasized.
O'Neill-Dee et al, 2019[8]	Investigate the exposure of psychoactive substances, including kratom in the United States	Exposure and use of kratom increased in the United States from 2000 to 2017. Among all psychoactive substances that have seen an increase in the rate of consumption, kratom had the highest percentage of serious medical outcomes and hospitalization rates due to toxicity or adverse side effects.
Dixon et al, 2019[22]	Investigate the contamination of kratom products	Marketing and sales of kratom products are unregulated. About 35% of the sample did not contain the manufacturer's information, and about 17% of products had *Salmonella* species.
Eggleston et al, 2019[23]	Determine the toxicity and safety of kratom	Kratom is associated with toxicities and deemed unsafe to use. Due to a lack of regulations, kratom supplements are considered a public health threat.
White, 2018[24]	Provide information to understand clinical use, adverse effects, and abuse potential of kratom	Kratom was found to have effects on α-2 and opioid receptors and has also shown anti-inflammatory effects. However, clinical data are unavailable to confirm its efficacy.
Henningfield et al, 2018[25]	Explore the abuse potential of kratom abuse	Kratom showed opioid-like effects with abuse potential. It can also cause respiratory depression.
Sethi et al, 2018[26]	Evaluate the potential of kratom abuse in comparison to opiates	Kratom is considered addictive. Users can develop tolerance and withdrawal symptoms similar to opioids. Since kratom is unregulated and legal, users tend to abuse it.
Grundmann, 2017[12]	Identify the beneficial and detrimental effects of kratom on the health of consumers and evaluate its dose-dependent effects	Kratom is used for treating pain and mental conditions and is mostly consumed by the middle-aged population. Dose-dependent side effects such as nausea and constipation were produced when consumed at high doses or frequently.
Fluyau and Revadigar, 2017[27]	Evaluate kratom use trends in the Western world and associated clinical risks	Use of kratom in the Western world is increasing. Due to the risk of its toxicity, the side effects outweigh any unproven or perceived benefits.
Anwar et al, 2016[13]	Study poison control data from the national database	Poison control centers observed a 10 times increase in adverse event calls due to side effects from 2010 to 2015. About one-third of the population used kratom voluntarily and nonaccidental. Health care professionals reported almost half of the reported adverse events. The most common symptoms were tachycardia, agitation, irritability, drowsiness, nausea, and hypertension.
Warner et al, 2016[28]	Study pharmacology, toxicology, and abuse potential of kratom	The deficit in current regulatory policies and laboratory techniques to detect the toxicity of kratom was highlighted.

details to protect consumers.[63] Kratom is considered illegal in countries such as Australia, Denmark, Finland, Israel, United Kingdom, Lithuania, Myanmar, Malaysia, Poland, Romania, South Korea, Sweden, and Thailand.[16,59,63]

In this review, we primarily used 5 databases as mentioned in the methodology section. Our thorough literature review covered all aspects of our research objectives and currently available research evidence. However, restricting the literature search to only 5 databases could be considered a limitation of our study, as we did not have full access to any other additional databases. Findings from our review are presented in Table 2.[7,8,12,13,22–28]

Challenges and Barriers

1. Animal studies have shown some potential in alleviating pain and managing symptoms of opioid withdrawal, yet no clinical trials completed in humans documented the safety and efficacy of kratom.
2. Although kratom lacks toxicities associated with classical opioids, concerns about safety and lack of quality control of products sold in the United States are legitimate.
3. There are no approved medical regimens to treat kratom addiction.
4. Plans to classify kratom as a Schedule I controlled substance might significantly hinder important research on kratom.

Recommendations

1. Sensitization health campaigns should be conducted to inform the public.
2. While kratom use is still legal in most regions of the United States, the safety concerns are legitimate and thus it should be used with discretion.
3. Large-scale, well-designed clinical trials are needed to assess and verify the safety, efficacy, and potential benefits and risks associated with kratom use.
4. Health care providers should be encouraged to participate in training and continuing medical education to keep up to date on kratom, its clinical implications, and drug interactions to assist patients in making informed decisions.
5. Strict enforcement of regulatory standards is necessary to ensure the appropriate and accurate labeling of kratom. Standardization of units across all available products is required to avoid toxicity and overdose.
6. The quality of the product must be verified and promoted through good manufacturing practices to keep adulterated and contaminated kratom products off the market.
7. Emerging health concerns due to kratom use should be critically analyzed in a broader context to understand its long-term implications on society with the help of benefit-risk ratio with regard to its use for alleviating opiate withdrawal symptoms.

CONCLUSION

While there has been increasing use of kratom by the public as an alternative for self-treatment of opioid withdrawal and pain, its full safety profile is unknown. Public perception of its safe use, efficacy, and toxicity needs to be substantiated with well-designed randomized clinical trials. Hence, discretion and caution are advised in the use of kratom and its products.

Submitted: July 27, 2020; accepted September 23, 2020.

Published online: February 18, 2021.

Potential conflicts of interest: None.

Funding/support: None.

REFERENCES

1. Müller CP, Schumann G. Drugs as instruments: a new framework for non-addictive psychoactive drug use. *Behav Brain Sci*. 2011;34(6):293–310.
2. Rosenbaum CD, Carreiro SP, Babu KM. Here today, gone tomorrow…and back again? A review of herbal marijuana alternatives (K2, spice), synthetic cathinones (bath salts), kratom, Salvia divinorum, methoxetamine, and piperazines. *J Med Toxicol*. 2012;8(1):15–32.
3. Streatfeild D. *Cocaine: An Unauthorised Biography*. New York, NY: St. Martin's Press; 2001.
4. Adkins JE, Boyer EW, McCurdy CR. Mitragyna speciosa, a psychoactive tree from Southeast Asia with opioid activity. *Curr Top Med Chem*. 2011;11(9):1165–1175.
5. Ingsathit A, Woratanarat P, Anukarahanonta T, et al. Prevalence of psychoactive drug use among drivers in Thailand: a roadside survey. *Accid Anal Prev*. 2009;41(3):474–478.
6. Singh D, Narayanan S, Vicknasingam B. Traditional and non-traditional uses of mitragynine (kratom): a survey of the literature. *Brain Res Bull*. 2016;126(Pt 1):41–46.
7. Veltri C, Grundmann O. Current perspectives on the impact of kratom use. *Subst Abuse Rehabil*. 2019;10:23–31.
8. O'Neill-Dee C, Spiller HA, Casavant MJ, et al. Natural psychoactive substance-related exposures reported to United States poison control centers, 2000–2017 [published online ahead of print November 25, 2019]. *Clin Toxicol (Phila)*.
9. The facts about kratom. Kratom Information and Resource Center. Updated September 1, 2020. Accessed September 5, 2020. https://kratominfocenter.org/the-facts-about-kratom/
10. Prozialeck WC, Jivan JK, Andurkar SV. Pharmacology of kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. *J Am Osteopath Assoc*. 2012;112(12):792–799.
11. Nicewonder JA, Buros AF, Veltri CA, et al. Distinct kratom user populations across the United States: a regional analysis based on an online survey. *Hum Psychopharmacol*. 2019;34(5):e2709.
12. Grundmann O. Patterns of kratom use and health impact in the US—results from an online survey. *Drug Alcohol Depend*. 2017;176:63–70.
13. 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(29):748–749.
14. Kratom DrugFacts. What is kratom? National Institute on Drug Abuse. Updated April 2019. Accessed July 1, 2020. www.drugabuse.gov/publications/drugfacts/kratom
15. Find Help. ATOD. Substance Abuse and Mental Health Services Administration. Updated April 23, 2020. Accessed July 1, 2020. https://www.samhsa.gov/find-help/atod
16. Eastlack SC, Cornett EM, Kaye AD. Kratom-pharmacology, clinical implications, and outlook: a comprehensive review. *Pain Ther*. 2020;9(1):55–69.
17. Likhitsathian S, Jiraporncharoen W, Aramrattana A, et al. Polydrug use among kratom users: findings from the 2011 Thailand National Household Survey. *J Subst Use*. 2018;23(4):384–389.
18. Suwanlert S. A study of kratom eaters in Thailand. *Bull Narc*. 1975;27(3):21–27.
19. Sethi R, Hoang N, Ravishankar DA, et al. Kratom (mitragyna speciosa): friend or foe? *Prim Care Companion CNS Disord*. 2020;22(1):19nr02507.
20. Substance Abuse and Mental Health Services Administration. 2019. Accessed July 2, 2020.

https://www.samhsa.gov/
21. Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
22. Dixon RB, Waggoner D, Davis M, et al. Contamination of some kratom products with salmonella. *Ann Clin Lab Sci*. 2019;49(5):675–677.
23. Eggleston W, Stoppacher R, Suen K, et al. Kratom use and toxicities in the United States. *Pharmacotherapy*. 2019;39(7):775–777.
24. White CM. Pharmacologic and clinical assessment of kratom. *Am J Health Syst Pharm*. 2018;75(5):261–267.
25. 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;235(2):573–589.
26. Sethi R, Miller KA, McAllister R. Kratom: is it the new illicit opiate on the market? *Prim Care Companion CNS Disord*. 2018;20(4):15l01895.
27. Fluyau D, Revadigar N. Biochemical benefits, diagnosis, and clinical risks evaluation of kratom. *Front Psychiatry*. 2017;8:62.
28. Warner ML, Kaufman NC, Grundmann O. The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. *Int J Legal Med*. 2016;130(1):127–138.
29. Addictive Substance Called Kratom Becoming Popular in South Florida. Partnership to End Addiction. Published July 6, 2011. Accessed July 3, 2020. https://drugfree.org/learn/drug-and-alcohol-news/addictive-substance-called-kratom-becoming-popular-in-south-florida/
30. Smith PA. Is Kratom a Performance Enhancer or a Lethal Opioid? Outside. Accessed July 3, 2020. https://www.outsideonline.com/2387546/kratom-safety
31. Modernizing Drug Death Data. Centers for Disease Control and Prevention. Updated April 9, 2019. Accessed July 3, 2020. https://www.cdc.gov/surveillance/projects/improving-data-on-drug-overdose-deaths.html
32. Yamamoto LT, Horie S, Takayama H, et al. Opioid receptor agonistic characteristics of mitragynine pseudoindoxyl in comparison with mitragynine derived from Thai medicinal plant Mitragyna speciosa. *Gen Pharmacol*. 1999;33(1):73–81.
33. Babu KM, McCurdy CR, Boyer EW. Opioid receptors and legal highs: Salvia divinorum and kratom. *Clin Toxicol (Phila)*. 2008;46(2):146–152.
34. Azizi J, Ismail S, Mordi MN, et al. In vitro and in vivo effects of three different mitragyna speciosa korth leaf extracts on phase II drug metabolizing enzymes—glutathione transferases (GSTs). *Molecules*. 2010;15(1):432–441.
35. Reagmongkhol CD, Keawpradup N, Sawangjaroen K. Effects of the extracts from mitragyna speciosa leaves on analgesic and neurobehavioural activities in experimental animals. *Songklanakarin J Sci Technol*. 2007;29(suppl 1):39–48.
36. Roche KM, Hart K, Sangalli B, et al. Kratom:a case of legal high. *Clin Toxicol*. 2008;46(7):598.
37. Nelsen JL, Lapoint J, Hodgman MJ, et al. Seizure and coma following kratom (mitragynina speciosa korth) exposure. *J Med Toxicol*. 2010;6(4):424–426.
38. Hillebrand J, Olszewski D, Sedefov R. Legal highs on the Internet. *Subst Use Misuse*. 2010;45(3):330–340.
39. Jansen KL, Prast CJ. Ethnopharmacology of kratom and the Mitragyna alkaloids. *J Ethnopharmacol*. 1988;23(1):115–119.
40. Hassan Z, Muzaimi M, Navaratnam V, et al. From Kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. *Neurosci Biobehav Rev*. 2013;37(2):138–151.
41. Hassan Z, Bosch OG, Singh D, et al. Novel psychoactive substances-recent progress on neuropharmacological mechanisms of action for selected drugs. *Front Psychiatry*. 2017;8:152.
42. Kong WM, Chik Z, Ramachandra M, et al. Evaluation of the effects of mitragyna speciosa alkaloid extract on cytochrome P450 enzymes using a high throughput assay. *Molecules*. 2011;16(9):7344–7356.
43. Porrogi P, Kóbori L, Kõhalmy K, et al. Limited applicability of 7-methoxy-4-trifluoromethylcoumarin as a CYP2C9-selective substrate. *Pharmacol Rep*. 2008;60(6):972–979.
44. Kikura-Hanajiri HR, Kawamura M, Maruyama T, et al. Simultaneous analysis of mitragynine, 7-hydroxylmitragynine and other alkaloids in the psychotropic plant "kratom" (mitragyna speciosa) by LC-ESI-MS. *Forensic Toxicol*. 2009;27:67–74.
45. Kratom. Drugs.com. Updated May 4, 2020. Accessed July 4, 2020. https://www.drugs.com/illicit/kratom.html
46. NIH US National Library of Medicine. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/results?cond=kratom&term=&cntry=&state=&city=&dist=. Accessed July 3, 2020.
47. Kruegel AC, Grundmann O. The medicinal chemistry and neuropharmacology of kratom: a preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. *Neuropharmacology*. 2018;134(Pt A):108–120.
48. Váradi A, Marrone GF, Palmer TC, et al. Mitragynine/corynantheidine pseudoindoxyls as opioid analgesics with mu agonism and delta antagonism, which do not recruit β-arrestin-2. *J Med Chem*. 2016;59(18):8381–8397.
49. Daly J. FDA Declares Kratom an Opioid. TheScientist. Published February 7, 2018. Accessed July 4, 2020. https://www.the-scientist.com/news-analysis/fda-declares-kratom-an-opioid-were-here-to-explain-what-it-does-30306
50. 2017 NSDUH Annual National Report. Substance Abuse and Mental Health Services Administration. Updated September 14, 2018. Accessed July 5, 2020. https://www.samhsa.gov/data/report/2017-nsduh-annual-national-report
51. Vivolo-Kantor AM, Seth P, Gladden RM, et al. Vital Signs: trends in emergency department visits for suspected opioid overdoses—United States, July 2016–September 2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(9):279–285.
52. Speciosa.org. Mississippi steps back from regulating or outlawing kratom. Botanical Education Alliance website. Accessed July 5, 2020. https://speciosa.org/category/activism/botanical-education-alliance/
53. The Authoritative Source For all Things Kratom. Kratom Science. Accessed July 5, 2020. https://www.kratomscience.com/
54. Arndt T, Claussen U, Güssregen B, et al. Kratom alkaloids and O-desmethyltramadol in urine of a "Krypton" herbal mixture consumer. *Forensic Sci Int*. 2011;208(1–3):47–52.
55. Khazaeli A, Jerry JM, Vazirian M. Treatment of withdrawal and addiction with buprenorphrine. *J Addict Med*. 2018;12(6):493–495.
56. How to treat Kratom Abuse and Withdrawal. American Addiction Centers. Updated November 13, 2019. Accessed July 5, 2020. https://americanaddictioncenters.org/kratom
57. Kratom drug profile. European Monitoring Centre for Drugs and Drug Addiction. Accessed July 5, 2020. http://www.emcdda.europa.eu/publications/drug-profiles/kratom
58. Kratom. United States Drug Enforcement Administration. Accessed July 6, 2020. https://www.dea.gov/factsheets/kratom
59. FDA and Kratom. US Food & Drug Administration. Updated September 11, 2019. Accessed July 6, 2020. https://www.fda.gov/news-events/public-health-focus/fda-and-kratom
60. Galbis-Reig D. A case report of kratom addiction and withdrawal. *WMJ*. 2016;115(1):49–52, quiz 53.
61. Sheleg SV, Collins GB. A coincidence of addiction to "Kratom" and severe primary hypothyroidism. *J Addict Med*. 2011;5(4):300–301.
62. Swetliz I. HHS recommends that DEA makes kratom a schedule 1 drug, like LSD or heroin. STAT. Published November 9, 2018. Accessed July 6, 2020. https://www.statnews.com/2018/11/09/hhs-recommended-dea-ban-kratom-documents-show/
63. Momentum Gains KCPA. in Mississippi and Oklahoma. American Kratom Association. Updated March 2, 2020. Accessed July 6, 2020. https://www.americankratom.org/advocacy/update/kcpa-momentum-gains-in-mississippi-and-oklahoma.html