

Current perspectives on the impact of Kratom use

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Abstract: The leaves from the tree *Mitragyna speciosa*, commonly known as Kratom, in the coffee plant family (Rubiaceae) are commonly used in their native habitat of Southeast Asia as a stimulant to sustain energy during hard day labor and as an opioid-like analgesic and sedative. Traditional and modern uses overlap based on the effects of the leaf extract which has also gained popularity in the United States and Europe in the last two decades. Kratom has and is being used for the mitigation of opioid withdrawal symptoms and as a harm reduction agent with a minority of users subsequently developing a dependence on the extract. The respective demographic use patterns of Kratom differ between Southeast Asia and the Western world. While pure Kratom is primarily used by day laborers and misused in conjunction with cough medicine by youth in Southeast Asia, a majority of users in the United States is middle-aged, has at least middle income, private health insurance, and completed some college. Deaths attributed to the use of Kratom have been reported in Europe and the United States but not in Southeast Asia. Although Kratom was detected as the alkaloid mitragynine in the blood of the decedents, causality could not be established in almost all cases because of poly-drug exposures. It is notable that Kratom can cause herb-drug interactions, especially with other central nervous system -active substances. Given the mostly unregulated market for Kratom products in Western countries, consumers may be exposed to adulterated or contaminated products, especially if purchased through websites or the darknet. A number of countries have scheduled Kratom because of its stimulant- and opioid-like effects and the established interaction of the alkaloid mitragynine with opioid receptors.

Keywords: Kratom, *Mitragyna speciosa*, use pattern, Southeast Asia, substance dependence

Introduction

Kratom (*Mitragyna speciosa* Korth.) is an evergreen tree in the coffee family (Rubiaceae) that is native to Southeast Asia and cultivated especially in Indonesia, Malaysia, and Thailand for its historical medical and recreational uses.¹ Kratom is also referred to as biak-biak, ketum, or Maeng Da in different regions and describes both the tree and the varying extracts and preparations derived from it.² The leaves of the tree, that are used for their pharmacological activity, can have different colored veins (white, green, or red) which are not distinguished in its native habitat but have been attributed to varying effects when sold as powdered leaf extracts in Western countries.³ The main active compounds of current interest are indole alkaloids, primarily mitragynine and 7-hydroxymitragynine that act as partial agonists on opioid receptors.⁴ Kratom products contain approximately 2% mitragynine and either none or between 0.01% and 0.02% 7-hydroxymitragynine.⁵ Among other mitragyna

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indole alkaloids, mitragynine presents with a unique mechanism of action and pharmacology distinct from classical opioids like morphine, heroin, or fentanyl. Binding to the μ -opioid receptor causes recruitment and activation of the G-protein-coupled signaling cascade but does not lead to recruitment of β -arrestin 2 which has been associated with many of the undesired effects of opioid receptor activation such as constipation, respiratory depression, and dependence.^{4,6} In animal models, mitragynine did not cause dependence or increased self-administration and even reduced prior administration of morphine whereas 7-hydroxymitragynine did present with a dependence liability.⁷

The use of Kratom in Southeast Asia has been documented back for at least 150 years and described both a stimulant effect for use in hard day labor when fresh leaves are chewed and an analgesic and relaxing effect if brewed into a tea.³ It also serves as a substitute and mitigation strategy for opium that was widely used in Malaysia and Thailand from the 1830s to the 1920s.³ In addition, Kratom remains in use for its antispasmodic, muscle-relaxant, and antidiarrheal effects while both its brief stimulant and analgesic effects remain a popular home remedy in Southeast Asia.^{8,9} The use of Kratom is prohibited in Malaysia under Poisons Act 1952, but its use remains widely spread because the tree grows natively and tea decoctions are readily available in local communities.¹ Thailand lifted the ban on the use, production, and possession of Kratom in 2018 for medicinal purposes.¹⁰

The increase of Kratom sales across Europe and North America caused rising concerns about its safety with several European countries banning the plant and its active alkaloids.¹¹ The status of Kratom as a dietary supplement remains vague in the United States as of this writing because the Food and Drug Administration (FDA) does not consider Kratom a recognized supplement that has been present on the US market prior to the enactment of the Dietary Supplement Health and Education Act (DSHEA) of 1994 that would have allowed for such a provision.¹² Instead, the FDA has designed mitragynine and 7-hydroxymitragynine as opioids and recommended placement of these compounds into the Controlled Substances Act Schedule I by the US Drug Enforcement Administration (DEA).¹³ As of this writing, this scheduling action has not taken place despite an earlier attempt by the agency to do so which was withdrawn based on public comments and the action by several members of the US congress. Several US states have either banned Kratom and its active alkaloid compounds or enacted laws that prohibit

the sales of adulterated products that are not appropriately labeled according to Good Manufacturing Practices.^{12,14}

Kratom users in the West are using the leaf extract and its varied formulations for a range of health reasons that primarily relate to chronic pain, mood disorders, or mitigating the withdrawal symptoms of a prescription or illicit drug dependency.¹⁵ Although the number of Kratom users in the United States remains vague, the estimate ranges from 3 to 5 million based on survey data and membership information provided by the American Kratom Association.¹⁶

This review provides a current perspective on the use pattern and impact of Kratom use on the individual and society. The implications of Kratom use are discussed both from the use as a traditional herb and supplement as well as a potential future medicine, either as a pure drug or complex natural extract.

Methods

PubMed and Google Scholar databases were searched on April 9, 2019, for all research and review articles covering Kratom use patterns. The initial search terms were: “Kratom” AND “use pattern” or “Kratom use pattern” or “Kratom” AND “misuse” or “Kratom” AND “abuse”. The search returned a total of 2,596 sources. Of these, 91 resulted from PubMed and 2,505 from Google Scholar searches. Both authors evaluated articles for inclusion in the review independently. Initially, duplicates were eliminated, reducing the total number of references to 2,364. Further exclusion of non-English literature resulted in further reduction of the number of references to 1,823. Following evaluation of references, a total of 467 references were initially deemed relevant to the topic of the review. Exclusion of several book chapters that referred back to primary literature and references that referred to original research articles narrowed the references to a total of 44 that were included in this narrative review.

Kratom use pattern in Southeast Asia

The first reported use of Kratom in the scientific literature dates back to 1836 when it was noted that the leaves of the tree were used by Malays as a substitute for opium.¹⁷ In addition, other observations documented the traditional use of Kratom leaves and its preparations as a wound poultice, for fever, and for mitigating the withdrawal symptoms from opium and later heroin.¹⁷ Its traditional use has not been dated and has likely been part of the social fabric for hundreds of years given that the tree grows indigenously throughout Malaysia, Thailand, and

Indonesia.⁸ Its use in Malaysia and Thailand has been primarily for two broad applications: as a stimulant to increase work efficiency, endurance, and tolerance to hot and humid climate conditions for manual laborers and as a medical remedy for a range of symptoms. The latter practice as a traditional medicine and home remedy primarily uses fresh or dried leaf material to prepare a decoction by brewing the leaves and ingesting it as a beverage either hot or cold. In this form, the effects have been primarily described as analgesic, relaxing, anti-diarrheal, antipyretic, and anti-diabetic.¹⁸ Far less common is smoking of the dried leaf although it is occasionally reported in Malaysia and associated with a relaxing effect.¹⁸

The most recent study investigating the prevalence of Kratom use was conducted in 2007 in Thailand among 26,633 respondents between the ages of 12 and 65 years.¹¹ The lifetime prevalence for Kratom use among all users was 2.3% which was higher than for marijuana use while 13- to 16-year-old students reported a 9.4% lifetime prevalence in a 2004 survey. Kratom is the most commonly used illicit drug in Thailand, and similar percentages are likely for Malaysia based on conducted seizures of Kratom. The high prevalence can be explained by the long history of use as both medicine and recreational drug, readily accessible plant material that grows natively in the area, and perceived safety of Kratom preparations.

Despite its traditional medical uses, Kratom dependence has been known and observed for a long time and is well documented.¹⁷ Unlike opium, opioid, or heroin addiction, Kratom addiction is not associated with a significant stigma in rural communities if a husband is taking it to support his family. However, female Kratom use is much less tolerated and there are far fewer female users in local communities.⁸

Scientific research on Kratom and its effects on users in Thailand and Malaysia has increased in the past 10 years given the rising interest in Kratom extracts in other countries. With a long use history and a socially acceptable tradition of use among the general population, human studies in general appear to be easier to conduct compared to Western countries although Kratom is illegal in Malaysia.

Given the long-term use of Kratom especially by day laborers to boost endurance and withstand physical labor and harsh work conditions, both the stimulant and opioid-like analgesic effects can contribute to dependence development and addiction.^{19,20} Two surveys conducted in Malaysia and Thailand reported that the average age of long-term Kratom users was in their mid-30s and a

majority were married with lower education levels.^{19,20} While Kratom is both used for its stimulant and opioid-like effects, a majority of users had a history of drug abuse and primarily used Kratom to mitigate opioid and stimulant withdrawal symptoms. It was not uncommon among survey respondents to develop a dependence on Kratom. Those with lower education attainment were more likely to successfully stop using Kratom compared to those with a higher level of education.²⁰ One potential explanation for this inverse correlation is the use of Kratom among higher educated individuals who had previously used a prescription opioid and are now either self-treating a pain condition or mitigating withdrawal symptoms from the former prescription drug. Maintaining the use of Kratom products can be relatively expensive which can correlate higher educational attainment with higher income to allow this habit. Another explanation could be the use of Kratom as a perceived “natural” alternative to prescription or “synthetic” drugs for the self-treatment of a health condition. The belief that “natural” equals safe is prevalent among more educated individuals despite a lack of support for such a statement especially in Western countries.

A cross-sectional survey investigated the correlation between amount and frequency of Kratom consumption and risk of dependence and addiction development in long-term users in three northern peninsular states of Malaysia.²¹ There was a correlation between increased consumption of Kratom and risk of dependency development, severity of withdrawal symptoms, and cravings for the extract. Physical withdrawal symptoms manifested as muscle spasms, diarrhea, lack of appetite, fever, pain, and runny eyes and nose. Psychological withdrawal was characterized by mood swings such as anger, nervousness, restlessness, disturbed sleep, tension, and sadness.²¹ Despite these findings that are similar to opioid withdrawal and craving symptoms, a majority of participants in surveys and case studies as well as their providers and caretakers do not characterize Kratom withdrawal and cravings as severe as those experienced during opioid withdrawal and those symptoms were of shorter duration.^{18,21,22} Although Kratom dependence is widespread, treatment admissions for withdrawal have increased in recent years from 1,000 in 2007 to almost 3,000 in 2011 in Thailand where Kratom accounts for approximately 2% of all drug treatment admissions.¹¹ It is not yet clear if this change is based on a stricter enforcement of drug policies and how it will change with the legalization of Kratom for medical purposes in 2018.

Even if Kratom dependence and withdrawal are not perceived to be as severe as for opioids, the question of impairment with the chronic use of Kratom remains. A study involving 70 regular Kratom users and 25 control participants evaluated cognitive functioning using the Cambridge Neuropsychological Test Automated Battery (CANTAB) found deficits with higher chronic Kratom consumption (more than 3 glasses of kratom decoction consumed per day) in new learning and visual episodic memory.²³ However, the authors conclude that overall Kratom users independent of the amount they consumed were comparable in their cognitive and executive functions to control participants and does not impair motor, memory, or attention function.

Kratom use and even dependence does not impair social functioning according to several studies conducted in Malaysia.^{9,24} A majority of chronic Kratom users are employed, married, and live with their family and rarely present with health problems. This stands in contrast to alcohol, opioids, or amphetamine abuse that are not accepted in society.²⁵

Aside from the traditional uses of pure Kratom for its medicinal properties and as an endurance enhancer for hard labor, newer preparations of the plant have emerged that are seen as problematic. Because of its bitter taste, Kratom tea preparations are often sweetened or mixed with beverages to make it more palatable.⁹ However, teenagers and young adults in urban areas do mix Kratom leaves and teas with caffeinated beverages such as Coca-Cola and cough syrup containing codeine or diphenhydramine. The mixture is boiled to create a syrup referred to as 4×100.⁹ In many cases, the syrup provides for a more intense euphoria and is often consumed together with other drugs such as an antidepressant, anxiolytic, alcohol, or analgesic. Poly-drug use with Kratom increases the risk of fatal additive or synergistic toxic effects whereas there have been no reports in Southeast Asia of fatalities caused by the ingestion of pure Kratom preparations.

Another folkloristic use of Kratom is as a potential aphrodisiac that has been reported in several surveys of chronic Kratom users.^{19,20} This activity contrasts with the opioid-like effects since classical opioids are commonly associated with sexual dysfunction and decreased libido. Direct measurement of testosterone, follicle-stimulating and luteinizing hormone did not indicate any differences between Kratom users and non-users although there were some non-pathological differences in blood profiles between the low-dose and high-dose Kratom users.²⁶

Furthermore, other studies and epidemiological data indicate that despite its use as an aphrodisiac and the potential for impairment, Kratom is not associated with an increased risk for sexually transmitted diseases or needle sharing.¹¹

Use pattern in the United States and Europe

Unlike Kratom use in Asia, emergence into the Western markets is a relatively new occurrence. Anecdotal reports suggest that immigrants from Southeast Asia first imported Kratom into the United States in the 1980s and 1990s with an expansion of use in the United States within the past decade.^{5,12} In the West, Kratom is sold through the Internet and at herbal stores, tobacco/smoke shops, and “head” shops where it is primarily marketed as an herbal medicine/supplement to treat a variety of ailments (pain, mental health, opioid withdrawal symptoms) as well as a “legal” or “natural” high and alternative to traditional opioids and even promoted as an “herbal speedball.”^{1,11,15,27–29}

Consumption of Kratom in the United States is predominantly by liquids, but the use of powders added to food or beverages and consumption of Kratom capsules is growing in popularity.¹² Users brew Kratom in a similar fashion as making tea or coffee where the leaf material (whole leaf or powder) is steeped in boiling water or cold extracted. Acids have been used to enhance the extraction. The resulting tea is bitter, so sugar, honey, or various sweeteners are often added.¹²

Because of the route of administration as an oral supplement, there is considerable discussion about the classification of Kratom. To date, there have been few reports of injections or other routes of administration that would indicate a higher degree of abuse and dependence. Furthermore, isolation of mitragynine or 7-hydroxymitragynine has not been attempted for misuse or abuse purposes in a fashion similar to morphine from opium. However, the legality of Kratom as a supplement with limited regulatory oversight has been challenged or restricted in several countries because of its opioid-like effects and the presence of compounds that interact with opioid receptors.

The legal status of Kratom varies in the West from region to region. While the European Union has open borders between members and a shared currency, the legal status of Kratom varies. Kratom is an illegal drug/substance in Denmark, Finland, Ireland, Latvia, Lithuania, Poland, Romania, and Sweden.³⁰ The legal status of Kratom in the

United Kingdom is complex. While Kratom or *M. speciosa* is not listed as a commonly encountered Schedule 1 controlled substance, it most likely falls under the term of “psychoactive substance” of the Psychoactive Substances Act 2016 in the United Kingdom.^{31,32}

Kratom is not scheduled under the US Controlled Substances Act; however, the DEA does not recognize any legitimate medical use for Kratom.²⁹ The DEA based its stance on the FDA warning that Kratom “should not be used to treat medical conditions, nor should it be used as alternative to prescription opioids,” and that the FDA finds no indication that Kratom is safe.³³ As of this writing, Kratom is legal in all US States except Arkansas, Alabama, Indiana, Rhode Island, Wisconsin, and Vermont and the District of Columbia. There are also city bans in Alton, IL; Columbus, MS; Denver, CO; Jerseyville, IL; San Diego, CA; and Sarasota, FL, as well as a county ban in Union County, MS.³⁴ Further legislation regulating, restricting, banning the use of Kratom or reversing such bans is pending in other jurisdictions.

There are relatively few studies describing Kratom use in the West compared to studies focused on use in Asia. An online anonymous survey in the United States was utilized to answer three questions: 1) Who is consuming Kratom and for what purpose? 2) What perceived beneficial and detrimental effects are reported by Kratom users if dose and frequency of consumption are considered? 3) Does Kratom present with an abuse potential and withdrawal symptoms?¹⁵ Analysis of the demographics of this survey found that US Kratom users are white non-Hispanic males between 31 and 50 years of age, married or partnered, employed with an annual household income of US\$35,000 or higher, have private health insurance, had at least some college education, and had used Kratom for more than one year but less than five years. Respondents predominantly identified Kratom use to relieve acute or chronic pain followed by use for an emotional or mental condition. Respondents identified increased energy, decreased pain, increased focus, less depressed mood, lower levels of anxiety, reduced or stopped the use of opioid painkillers, reduction of PTSD symptoms, and elevated mood as beneficial effects of their Kratom consumption. Self-reported detrimental effects appeared to be dose-dependent and included nausea, constipation, and dizziness or drowsiness as the most frequently identified negative effects. Doses of up to 5 g of Kratom presented with lower odds ratios for detrimental effects than doses

of 8 g or more. Less than half of the respondents reported withdrawal effects within 12–48 hrs after discontinuation of Kratom and the withdrawal symptoms were mainly rated at a 2 or 3 on a 5-point Likert scale (from 1-severe to 5-not severe at all). This study shows that the US Kratom user population is diverse in demographics and motives for Kratom consumption and that doses of up to 5 g consumed 3 times per day were able to provide beneficial effects while having lower rates of negative effects.

Cinisi and colleagues evaluated literature from 1967 to 2015 to better understand Kratom pharmacology, Kratom use cross-culturally, experience of the user, and to identify risks and side effects related to Kratom consumption.¹¹ Their analysis identified a growing popularity of Kratom use in areas outside of Southeast Asia, specifically the European Union and United States. The increase in Kratom consumption in the European Union and United States corresponds to an increasing availability of Kratom for sale through the Internet. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) conducted an Internet survey of 27 European online shops in 2008 that identified Kratom as one of the most widely offered “legal highs” along with *Salvia divinorum*, Hawaiian Baby Woodrose seeds, Spice, and stimulant-containing capsules.³⁵ A more extensive study by the EMCDDA in 2011 showed Kratom as the most widely offered product with 20% of the online retailers shipping it to the European Union.³⁵ More studies are necessary to help understand the impact of Kratom as its use increases in the West, especially if Kratom follows the pattern of novel psychoactive drugs.^{11,36}

The increasing trend in Kratom consumption in the West has corresponded with an increase in reports of Kratom-related exposures to Poison Control Centers in the United States, care received at a health care facility due to Kratom consumption, and association with overdose fatalities.^{12,37–39} A retrospective analysis of poison center charts collected from January 1, 2002, to November 30, 2016, in the electronic database Toxicall™ using the keywords Kratom and *M. speciosa* was performed to summarize the clinical effects of Kratom.³⁹ The study evaluated 12 cases of Kratom exposure (dose and frequency were largely unknown) reported from health care facilities and described the clinical effects to include altered mental status, agitation, central nervous system depression, seizures, and tachycardia.³⁹ Admission to psychiatry and benzodiazepines were the most frequent treatment methods and no deaths were reported.³⁹ A larger analysis of

data reported to Poison Control Centers using the National Poison Data System database from 2011 to 2017 identified 1,174 Kratom-only exposures where 1,020 cases resulted in one or more clinical effects.³⁸ The most common clinical effects reported were agitation/irritability, tachycardia, nausea, drowsiness/lethargy, vomiting, confusion, and hypertension.³⁸ Serious clinical effects included seizures, respiratory depression, coma, increased bilirubin, bradycardia, rhabdomyolysis, renal failure, respiratory arrest, cardiac arrest/asystole, and cyanosis.³⁸ More than half (51.9%) of these cases received one or more therapies which included IV fluids, benzodiazepines, oxygen, naloxone, and tracheal intubation.³⁸

The national poison center reporting database documented 1,807 calls related to Kratom exposure from 2011 to 2017.³⁷ The Centers for Disease Control and Prevention analyzed data on unintentional and undetermined opioid overdose deaths from the State Unintentional Drug Overdose Reporting System.³⁷ Kratom was detected on postmortem toxicology testing in 152 cases of 27,338 overdose deaths from data collected from 11 states during July 2016–June 2017 and 27 states during July–December 2017.³⁷ Kratom was identified as the cause of death by a medical examiner in 91 of the 152 Kratom-positive deaths, but was the only identified substance in just seven of these cases.³⁷ Presence of additional substances in these seven Kratom-only cases cannot be ruled out.^{37,40} The co-occurring substances in the 91 cases where Kratom was identified as the cause of death include fentanyl (including analogs), heroin, benzodiazepines, prescription opioids, cocaine, and alcohol.³⁷ Multi-substance exposures involving Kratom, predominantly in combination with opioids, are associated with a greater odds ratio of admittance to a health care facility and occurrence of a serious medical outcome when compared to Kratom-only exposure.³⁸ These data highlight that Kratom use is associated with a complex population of poly-drug users and especially with opioid use disorder. These data further suggest that a deeper investigation into the toxicity of Kratom is needed, especially focusing on drug–herb interactions.

Kratom–drug interactions are further indicated in several case reports resulting in hepatotoxicity or death.^{41–45} A 70-year-old man with a history of hypertension and osteoarthritis, treated with amlodipine and oxycodone, presented with jaundice.⁴² The patient admitted to consuming Kratom twice daily for 4 days approximately 2–3 weeks before his initial presentation at a medical center for

jaundice.⁴² He presented with elevated creatinine (2.3 mg/dL) and total bilirubin levels (33.7 mg/dL) and clinically improved with supportive care, but required a readmission at which time he received 3 units of packed red cell transfusion to treat anemia.⁴² His abnormal liver tests normalized after three months, except his creatinine level remained slightly elevated (1.8 mg/dL).⁴² The liver damage in this case is most likely due to an amlodipine–kratom interaction involving the enzyme cytochrome P450 3A4 (CYP3A4).^{46,47}

The elderly are not the only individuals at risk of adverse events due to drug–kratom interactions. A 32-year-old male with a history of hypertension, anxiety, and lower back pain presented to an Emergency Department with jaundice, nausea, fatigue, joint pain, and night sweats after completing a dose of 60 Kratom tablets over 1 week (as per recommended dose on the bottle) and had mitragynine (47.8 ng/mL) and 7-hydroxymitragynine present in his urine.⁴⁵ The patient's history includes alcohol use and acetaminophen use for his back pain, but he has no history of smoking or illicit drug use. The patient received a loading dose of N-acetylcysteine (150 mg/kg/hr) but developed an anaphylactic response and further doses withheld. While the patient's liver enzymes were trending down, he was discharged prior to them normalizing. The authors attributed the acute liver injury solely to the patient's use of Kratom;⁴⁵ however, the repeated use of acetaminophen could have attributed to the liver injury and the consumption of Kratom could have been overwhelming to an already damaged liver.

Hepatotoxicity associated with Kratom use is rare and appear to be associated with chronic or high consumption of the product.⁴⁸ In animal experiments, high concentrations of mitragynine (100 mg/kg) or a methanolic Kratom extract (1000 mg/kg) in rats showed organ damage primarily to the kidneys and liver with elevated liver enzymes and hepatic cellular damage. Although these doses exceed both acute and chronic human doses, further research on the impact of chronic kratom consumption on liver and kidney function is warranted.

Kratom use could have serious adverse events due to drug–herb interactions, specifically with the antipsychotic quetiapine. A 27-year-old male with a history of Asperger Syndrome, bipolar disorder, and substance abuse was found deceased.⁴³ The postmortem analysis of subclavian blood revealed valproic acid (8.8 µg/mL), quetiapine (12,000 ng/mL), and mitragynine (qualitatively positive).⁴³ The death was ruled an accident and

due to acute toxic effects of quetiapine.⁴³ The high levels of quetiapine were ruled to be due to a drug–herb interaction with Kratom since there was no evidence of significant discrepancies in quetiapine pill quantities in his residence.⁴³ This case further highlights the need for more investigation into Kratom–drug interactions, specifically involving CYP2D6 and CYP3A4.

A better understanding of Kratom–drug interactions is needed specifically when dealing with consumption of Kratom to aid with withdrawal symptoms from, or as a substitute for, traditional opioids. Individuals suffering from opioid addiction are using Kratom out of curiosity and ease of purchasing.^{49,50} These individuals are highly variable and have an extensive substance use history.⁴⁹ The variability in both user and drug use/preference will further complicate developing a treatment plan and dealing with patients consuming Kratom. It is necessary for scientists to further elucidate Kratom drug–herb interactions to aid physicians who can then better educate their patients about the potential benefits and harms associated with Kratom through a more open dialog.

Discussion and conclusion

The traditional and current diverse uses of Kratom in both Southeast Asia and the Western world indicate that the impact of the leaf and its extracts are of multidimensional complexity including sociocultural, economic, medico-legal, and often individual issues. Throughout its history of use, Kratom has been known to exert stimulant- and opioid-like effects that is raising concerns with regulatory agencies and resulted in scheduling actions in various countries. Although knowledge from clinical studies is limited, epidemiological data obtained from Southeast Asia, Europe, and the United States indicate that Kratom has a distinct user profile and presents with discrete effects from other stimulants or opioids. A substance-dependent opioid user does not prefer Kratom over another opioid but instead would utilize Kratom as a harm reduction or mitigation agent. This has been the conclusion from studies in Malaysia and the United States although the current information is preliminary in scope based on the small sample sizes and regional limitation of the surveys. The findings do align with preclinical observations in rodents that report a reduction in morphine self-administration with the use of mitragynine. This current knowledge points to a potential for further development of mitragynine or use of Kratom as a harm reduction agent similar to methadone or buprenorphine.

This will have to be further studied under controlled clinical conditions.

The toxicity of Kratom remains a topic of discussion. From the CDC report and published cases, it is clear that Kratom has the potential to cause herb–drug interactions and even be involved in fatalities. While a majority of regular Kratom users in Southeast Asia and the West alike do not experience acute or chronic adverse effects, the incidence of unwanted side effects remains unknown and can include both stimulant and opioid-like sedative effects. Although some regulatory agencies, including the US FDA, have determined that Kratom and the alkaloids mitragynine and 7-hydroxymitragynine are opioids and thus should not be available without regulation, a direct causative link between the fatalities in which Kratom was detected cannot be drawn because nearly all of them involved poly-drug exposures.⁵¹ The toxicity of Kratom in various animal species is variable and has not been determined for most of them following acute and chronic exposure. The only clinical pharmacokinetic study in humans that provides blood concentrations of mitragynine does not correlate with post-mortem blood mitragynine concentrations thus not allowing for the determination of a toxic or lethal cut-off level. In addition, at this point, only the concentration of mitragynine is reported as indication of the presence of Kratom while it is not clear that mitragynine is in fact the toxic compound.

Reports and studies of the dependence potential to Kratom are of serious concern given the current opioid crisis in the United States and rising abuse of opioids in other countries. It appears that a majority of Kratom-dependent users had a prior substance use disorder or were seeking relief from a chronic pain condition but wanted to avoid opioid use. The severity of Kratom dependence symptoms appears to be milder compared to opioid use disorder and can be treated in a similar manner with buprenorphine or methadone and subsequent tapering. The incidence of Kratom dependency is not known and to date no US nationwide reporting system such as the National Survey on Drug Use and Health (NSDUH) or Monitoring the Future have indicated the use of Kratom in their reports.

Given the diversity in patterns of use for Kratom, additional research is paramount to support and expand on current findings. The labeling of Kratom products available to consumers needs to follow appropriate regulatory standards as well as quality good manufacturing practices to ensure that consumers who seek out

Kratom are not exposed to adulterated or contaminated products.⁵¹ Health care providers should be trained on the science of Kratom and its clinical implications to assist consumers in making the right choice and avoid herb–drug interactions.

Disclosure

The authors report no conflicts of interest in this work.

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