

Kratom (*Mitragyna speciosa*) Study

On the Public Health Risks and Recommendations

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Introduction

This report presents scientific evidence and issues surrounding use of kratom (*Mitragyna speciosa*), and offers a recommendation regarding the scheduling of kratom as a controlled substance.

Information from scientific articles and information of availability, use and perception from the public, media and users is presented. Any information directly copied from a source is presented in italics. To avoid crowding the text of the report with references, a summary of references is presented at the end of the report. This is a comprehensive list and not all of the references were accessed.



Section 1 – Background and Origins of Use



Mitragyna speciosa is a tree in the coffee family of Rubiaceae that grows in South East Asia, Philippines and New Guinea. In Thailand, the tree and the extracts from its leaves are called kratom. In South East Asia kratom has been used for a long time, with the leaves being chewed or prepared as a tea. They are rarely smoked. A low dose of kratom was used as a stimulant by indigenous people to overcome fatigue from working in the fields for long hours. At higher doses, it was used as a sedative similar to narcotics. In fact, it was also used by traditional healers as a substitute for opium.

The plant was named mitragyna by a Dutch botanist because of the similarity of the flower with a bishop's hat (miter). Other names for kratom are:

- Kakum
- Ketum
- Ithang
- Thom
- Biak



In the early 2000s, products labelled as 'kratom acetate' or 'mitragynine acetate' became available in Europe, although it was found that neither of them contained mitragynine. Caffeine and synthetic O-desmethylnaloxone (an active metabolite of naloxone) were found in products under the name '**krypton**'. More recently, products containing kratom have been sold as 'incense' for their psychoactive effects, but concentrations of the active components mitragynine and 7-hydroxymitragynine in these products differ depending on the variety of the plant used, the environment and the time of harvesting.

Section 2 – Mitragynine

2.1 – Chemical Structure

More than 40 chemical compounds have been isolated from the kratom leaf, including several alkaloids. An alkaloid is any of a class of nitrogenous organic compounds of plant origin that have pronounced physiological actions on humans. Mitragynine is the most common alkaloid found in the leaves.

Mitragynine is not soluble in water but dissolves easily in organic solvents such as acetone, alcohols, chloroform. Mitragynine is distilled at 230–240 °C under 5 mm of Hg. Purified, it consists of white crystals that melt at 102–106 °C. 7-hydroxymitragynine is found in small concentrations in kratom leaves. Mitragynine can be used to produce 7-hydroxymitragynine which is more powerful than simple mitragynine.

2.2 – Physical Appearance

Kratom is usually sold as leaves, dried and crushed or pulverized in a greenish powder. Powders are sometimes enhanced by leaf extracts. Pasty extracts and a brownish resin are prepared by boiling an aqueous preparation of leaves. Boiling eliminates the water content. Capsules filled up with powder are also available.

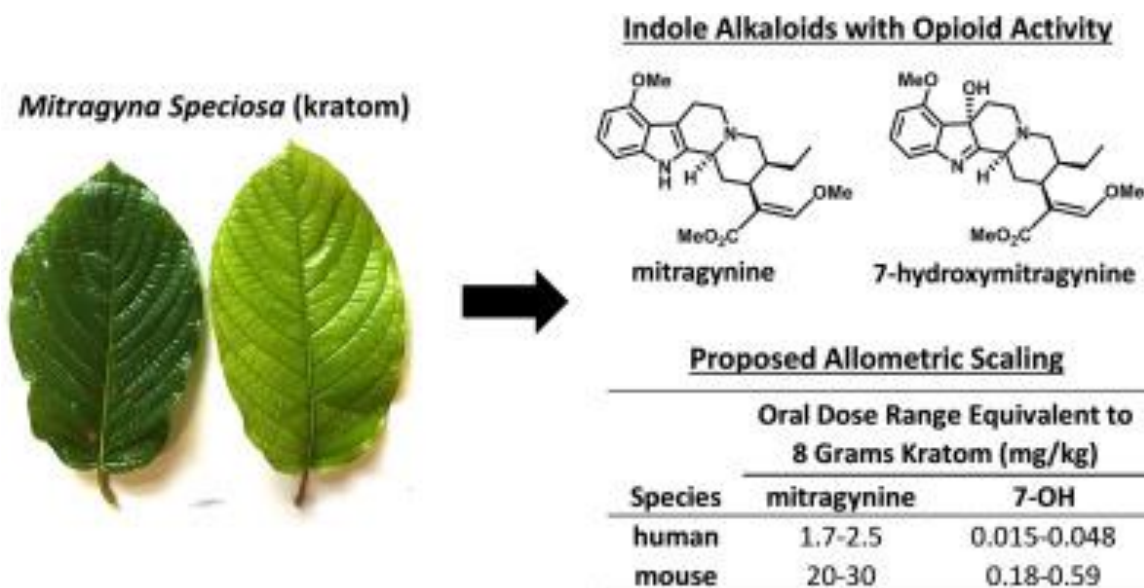


Section 3 – Pharmacology

3.1 – Dosage

Traditionally, fresh or dried kratom leaves are chewed, brewed into a tea or smoked. Kratom capsules sold in the U.S. generally contain approximately 80 mg of ground dry kratom leaf. In contrast, chewing 30 dry leaves per day weighing approximately 0.43 grams each results in chewing of 12.9 g of kratom per day which is equivalent to the amount of kratom in 161 capsules as typically sold in the U.S.

| Product | Quantity | Kratom Grams | Kratom Milligrams | Mitragynine Milligram | 7OHmitragynine Milligram |
|-----------------------------|--------------|--------------|-------------------|-----------------------|--------------------------|
| One green leaf | | 1.70 g | 170,000 mg | | |
| One dry leaf | | 0.43 g | 4,300 mg | | |
| One US capsule | | 0.080 g | 80 mg | 0.8 mg | |
| Low Thai daily consumption | 10 leaves | 17 g | | 120 to 200 mg | |
| High Thai daily consumption | 20-30 leaves | 30 to 50 g | | 240 to 400 mg | |
| One gram of dry leaf | | | | 10 to 20 mg | 0.10 -0.40 mg |
| 250 mL of fresh Thai drink | | | | 25 mg | |



3.2-Health Effects

3.2.1-Direct Effects

Mitragynine and 7-hydroxymitragynine, which are the main active ingredients of kratom, are selective agonists of the opioid receptor type μ -opioid receptor. Activation of the μ -opioid receptor by an agonist such as mitragynine causes analgesia (pain relief), sedation, slightly reduced blood pressure, itching, nausea, euphoria, decreased respiration, miosis, and decreased bowel motility often leading to constipation. Some of these effects, such as analgesia, sedation, euphoria, itching and decreased respiration, tend to lessen with continued use as tolerance develops. Miosis and reduced bowel motility tend to persist; little tolerance develops to these effects. Alpha2-adrenergic post synaptic receptors and the the calcium channels are also involved in the pharmacologic activity of mitragynine. The agonist effect of mitragynine is inhibited by naloxone. Kratom is virtually incapable of causing respiratory depression or many of the other negative effects of other opioids. Although mitragynine agonizes μ -opioid receptors, respiratory depression, coma, pulmonary edema and death have not been associated with human kratom ingestion.

What has been reported about the effects of kratom indicate differing effects according to dose. Small doses cause a stimulating effect while larger doses produces narcotic-sedative effects similar to morphine. After ingesting a few grams of dried leaves, stimulation and euphoria usually set in 10 minutes and last around one hour. Consumers are able to work more intensely than usual and become more sociable. In one of the rare experiments in humans, 50 mg of mitragynine caused both motor stimulation and vertigo, with loss of motor coordination and tremors of face and extremities. The exact mechanism behind the stimulating effect is not well understood.

Heavy users of kratom often lose weight, become tired and suffer constipation. Facial redness can also occur. Repeated doses of 10 to 25g of dried leaves cause perspiration, dizziness, nausea, and dysphoria (a state of unease or generalized dissatisfaction with life), which become quickly replaced by a state of calm, euphoria and dreaming state which may last up to 6 hours. Miosis (pupil contraction) is common.

Nausea
Vomiting
Constipation
Dry mouth
Loss of appetite
Sweating
Increased urination
Seizures
Hallucinations

3.2.2-Addiction and Dependency

Like other drugs with opioid-like effects, kratom might cause dependence, which means users will feel physical withdrawal symptoms when they stop taking the drug. Weaning symptoms are usually mild and

| |
|-------------------|
| Muscle aches |
| Insomnia |
| Irritability |
| Hostility |
| Aggression |
| Emotional changes |
| Runny nose |

tend to diminish in about one week. Hunger, lethargy, anxiety, hyper-excitability, rhinorrhea, nausea, perspiration, myalgia, tremors, involuntary gestures, sleepiness disorders and hallucinations may occur.

There are no specific medical treatments for kratom addiction. At least one report has demonstrated the efficacy of buprenorphine-naloxone (a treatment used to treat opioid dependence) in treating kratom dependence. Some people seeking treatment have found behavioral therapy to be helpful. Most cases that researchers have documented portray withdrawals as fairly manageable, with pain and trouble sleeping described as the most unbearable symptoms. One study published in the *Journal of Psychoactive Drugs* noted, “these effects appeared to be relatively mild, since the majority of the participants did not seek treatment for their pain and sleep problems and, in fact, the withdrawal effects only lasted between one and three days.

3.3-Interactions

Consumption of kratom and other drugs could cause very severe health effects. Interactions have been identified in humans between kratom tea and the following:

- Carisoprodol (or Soma ® a centrally acting skeletal muscle relaxant of the carbamate class);
- Modafinil (Provigil ® used to treat excessive sleepiness caused by certain sleep disorders. This includes narcolepsy, sleep apnea, and shift work sleep disorder);
- Propylhexédrine (Benzedrex ®, Obesin ® used as a nasal decongestant, appetite suppressant, and psychostimulant medication, analogue of methamphetamine); and
- *Datura stramonium* (jimsonweed or devil's snare, used in traditional medicine to relieve asthma symptoms. It is also a powerful hallucinogen and deliriant, used for the intense visions it produces).

Fatalities in the US were caused by a mixture of kratom, fentanyl, diphenhydramine, caffeine and of morphine.

3.4-Deaths

In 2017, the Food and Drug Agency (FDA) began issuing a warnings about kratom and now identifies 44 to 47 deaths related to its use, with at least one case being investigated as possible use of pure kratom. Most kratom associated deaths appear to have resulted from adulterated products (other drugs mixed in with the kratom) or taking kratom with other potent substances, including illicit drugs, opioids, benzodiazepines, alcohol, gabapentin, and over-the-counter medications, such as cough syrup. Also, there have been some reports of kratom packaged as herbal supplements or dietary ingredients that were laced with other compounds that caused deaths. See Appendix A for FDA Commissioner Scott Gottlieb, M.D.,’s statement on the agency’s scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse.

3.5-Other Adverse Events

Kratom use has also been associated with a national Salmonella outbreak that spanned January, 2017 to May, 2018 and affected at least 199 people ranging in age from less than 1 to 75. While no deaths were

reported, more than a third of infected individuals required hospitalization. The kratom products associated with this outbreak were purchased throughout the country; and, while the CDC has declared the outbreak investigation over, no kratom products were recalled as a result.

As infected kratom products may still be available for purchase, and the overall safety and quality control of the production of kratom cannot be assured, the U.S. Food and Drug Administration has warned consumers of the risk of Salmonella infection from contaminated kratom products.

3.6-Dearth of Sound Scientific Information

A 2015 study by Cinosi, et. al., stated that the relevant pharmacological data and peer-reviewed toxicological information was insufficient to reach definitive assessment of the safety in using kratom.

"Kratom pharmacology is complex and requires future research. This compound, in fact, acts on opioid as well as on dopaminergic, serotonergic, GABAergic and adrenergic systems. Therefore, subjective effects are very peculiar and range from psychostimulant to sedative-narcotic. Pharmacological mechanisms responsible for several of its alkaloids' activity deserve to be clearly established in future studies. ... On the other hand, online reports about kratom seem genuine and many users illustrate their detailed experiences as proper experiments on themselves. Thus, in the lack of relevant peer-reviewed data, the online monitoring seems to be indeed a very useful method to obtain preliminary information about new and emergent phenomena. Further, as demonstrated by the outcomes of this study, a better international collaboration is necessary to tackle this rapidly growing drug trend"

4-Medical Use

There are 10 species of *Mitragyna* (6 in SE Asia and 4 in Africa) known to be used in traditional medicine. But only *Mytragyna speciosa* has these stimulating/sedative effects. In South East Asia kratom is used as an anti-diarrheic, antitussive, antidiabetic, anti-helminthic drug, cure for heroin users and poultice for wounds. Outside of South East Asia it is used to treat chronic pain or alleviate opioid user withdrawal syndrome.

Mytragynine has no approved applications in modern western medicine. In recent years, some people have used kratom as an herbal alternative to medical treatment in attempts to control withdrawal symptoms and cravings caused by addiction to opioids or to other addictive substances such as alcohol. There is no scientific evidence that kratom is effective or safe for this purpose; further research is needed.

5-Epidemiology

5.1-Prevalence

Since this drug was recently introduced to the international market, there are few data on its use. An estimated five million people use kratom regularly, according to the American Kratom Association (AKA), a pro-kratom lobbyist group (<http://blogs.discovermagazine.com/crux/2018/11/15/kratom-effects-safety-made-illegal/#.XHMj4TNKhPY>).

5.2-Poison Control Studies

According to Forrester (2013), 14 kratom exposures were reported to Texas poison centers between 2009 and 2013. For comparison, it should be noted that during 2012, a total of 474 synthetic cannabinoid (e.g.,

K2, Spice) and 160 synthetic cathinone (e.g., bath salts) exposures were reported to Texas poison centers. This suggests that, even though the number of reported kratom exposures may have increased in recent years, its impact on poison centers is small compared with new substances of abuse.

Between January 2010 and December 2015, 660 calls reporting exposure to kratom were received by poison centers and uploaded to the National Poison Data System (NPDS). The NPDS serves all 50 United States, the District of Columbia and Puerto Rico and collects information from call reports made by both the public and health care providers. The number of calls per year between 2010 and 2015 increased tenfold from 26 calls in 2010 to 263 calls in 2015. There were an average of 110 calls per year which represents about 0.004 % of the approximately 3 million calls received by poison control centers each year.

According to the CDC, medical outcomes from those whose kratom use was reported to poison control centers were moderate or major for nearly half of cases (Mehruha et al, 2016). Typically, reported symptoms included rapid heart rate, agitation or irritability, drowsiness, nausea, and high blood pressure. One death was reported in a person who was exposed to the medications paroxetine (an antidepressant) and lamotrigine (an anticonvulsant and mood stabilizer) in addition to kratom. However, due to multiple substances involved in this matter, there was insufficient toxicological evidence to conclude that kratom played a causative role.

5.3-Louisiana Early Events Detection System (LEEDS)

The Louisiana Early Event Detection System (LEEDS) is a web-based reporting system that automatically processes hospital Emergency Department and Urgent Care data to identify visits indicative of specific syndromes tracked by the Louisiana Office of Public Health (OPH). LEEDS electronically tracks chief complaints from 60 hospital emergency departments which represent 35,000 to 40,000 visits per year. LEEDS tracks numerous syndromes and is used by Infectious Disease Epidemiology for important public health surveillance activities.

Out of 35,000 visits there were only 5 instances of tracking the word “kratom”. These were one allergic reaction, one “kratom withdrawal”, one for minor health effects from use of kratom and muscle relaxant, one with a cyanotic reaction after ingesting alcohol and 3 spoonful of kratom. None of these five cases were hospitalized and were discharged from the ED.

6-Marketing and Public Perception

6.1-Availability and Marketing

Kratom is heavily advertised on the internet. A google search displays several pages with advertisement on location, price and benefits of kratom use mixed with pages on the dangers of kratom.

Here are a few examples of advertisement / marketing easily viewable on the web. This is shown in this report to show the kind of information being publicly available. Evidently some readers will embrace these statements. Kratom is often advertised as a milder herbal remedy for a whole variety of ailment.

- *XXX kratom is a magical herb to boost a person's mental health and good news is it is the most affordable herb and kratom box is a place where you will find best versions of XXX kratom and all the herbal remedies.*

- It is a favorite brand of many people because of wide variety of strains which are curing mental health of people effectively, if you are tired of dealing with fatigue, too much stress, depression and anxiety try using XXX kratom to have a perfect relaxation of the mind and body.
- Using heavy drugs to get relief from pain is not a good idea you will ultimately get used to these drugs that they have long term destroying effects on you rather than curing you. On this site XXX remedies are introduced so you can cure your health without damaging it further, any person can try these remedies and get high time benefits through them.
- These remedies have such a great response from people and they have become very popular among them, they are available in fewer prices and you can get them in just 25 dollars and 250 grams in it.
- They have the best shipping time also as it will be delivered to you on the same day you make the order no matter where in the world you are living expect the product arrive to your door step on time.

6.2-Media Environment

Kratom has attracted a lot of media attention. Here is an example of an article published in a local Louisiana journal.



DEA Officially Backtracks On Move To Ban Kratom, An Herb Many Use As Medicine. The cases include a suicide and a drug overdose victim who tested positive for nine different substances. By Nick Wing

After intense backlash, the agency is making an unprecedented move to reconsider prohibition. The U.S. Drug Enforcement Administration appeared to concede Wednesday that it had been too hasty in attempting to ram

through a controversial ban on the herbal supplement kratom.

In a notice set to be published in the Federal Register, the DEA said it has formally withdrawn an August announcement that initially outlined plans to place mitragynine and 7-hydroxymitragynine, two active compounds in kratom, in Schedule I. Schedule I drugs include heroin and LSD and are considered to have no known medical benefit and a high potential for abuse.

Citing widespread backlash from kratom users, advocates and other stakeholders, the DEA says it will open an official comment period, set to end on Dec. 1. It is also asking the U.S. Food and Drug Administration for a formal scientific and medical evaluation of the herb, which will be used to make an updated scheduling recommendation.

*Kratom is an herb made from the leaves of *Mitragyna speciosa*, a Southeast Asian tree related to coffee. The alkaloids mitragynine and 7-hydroxymitragynine appear to activate opioid receptors in the brain and reduce pain. And although most opioids have sedative qualities, low to moderate doses of kratom actually serve as a mild stimulant.*

All of this has made kratom a popular traditional medicine for millennia in Asia and more recently in the West, where many users tout it not just as an analgesic, but also as a treatment for anxiety, depression and opioid addiction.

But the DEA has raised concerns about kratom's addictive potential, as well as isolated reports of harm associated with use. The agency's change in course will keep kratom legal for the immediate future, but it's unclear how long the delay will last.

The DEA will take submitted comments and the FDA's findings into consideration as it decides how to proceed. If it determines after Dec. 1 that there is "substantial evidence of potential for abuse to support" scheduling kratom, the agency can take additional action through the permanent or temporary scheduling process. To ban kratom on a permanent basis, the DEA would need to submit an additional notice of proposed rulemaking, which would allow for further input from the public and lawmakers.

But if the DEA maintains, as it did in August, that emergency scheduling of kratom is "necessary to avoid an imminent hazard to the public safety," it could file a new notice of intent, which would likely go into effect a month later. The agency could also opt to pursue both emergency and permanent scheduling simultaneously, or to leave kratom unregulated.

7-Legal Environment

7.1-Federal Controlled Substance Act

The question of whether Kratom is legal is determined by the Federal Controlled Substances Act (CSA). This Act sets out parameters for regulating different drugs and narcotics, categorizing them into several schedules based on their potential for abuse. Kratom leaves and the alkaloids found in this plant are not currently listed on any of these schedules, nor have they ever been. This means that possession of Kratom is not a crime and you do not need a prescription in order to buy or use it. There are also no laws put in place that would make it illegal to sell this plant or its byproducts under the CSA. In other words, Kratom is legal to buy, sell, possess, use, import, export, process and market in the United States.

7.2-Food and Drug Agency

Despite being a legal substance in the US, *Mitragyna Speciosa* has not been approved by the FDA for human consumption. This means it cannot be sold as a product intended to be ingested by humans. A supplier may not be able to label the product as a health supplement or a natural remedy and they are not allowed to promote the benefits of Kratom plants for energy, mood and relaxation.

7.3- Dietary Supplement Health and Education Act

The FDA regulates both finished dietary supplement products and dietary ingredients. The FDA regulates dietary supplements under a different set of regulations than those covering "conventional" foods and drug products. Under the Dietary Supplement Health and Education Act of 1994 (DSHEA):

Manufacturers and distributors of dietary supplements and dietary ingredients are prohibited from marketing products that are adulterated or misbranded. That means that these firms are responsible for evaluating the safety and labeling of their products before marketing to ensure that they meet all the requirements of DSHEA and FDA regulations.

It has been argued that placing kratom under the DSHEA would not be effective because kratom would not qualify as a dietary supplement and supplement manufacturers are not required to demonstrate supplements safety before marketing the supplements. The FDA can only ban a supplement if the FDA finds proof that the supplement is dangerous. This means that unsafe or ineffective supplements can be sold freely, while the FDA has only a limited capacity to monitor adverse reactions from supplements.

7.4-Drug Enforcement Administration

The DEA has listed Kratom as a “Drug and Chemical of Concern.” In late 2016, out of concern for public safety, the DEA placed a temporary ban on kratom. The Agency’s move was followed by a substantial negative reaction from kratom supporters and was quickly rescinded. As of April 2017, the DEA did not have a timetable for banning or scheduling the drug, though some states have banned it. But the (DEA) was initially moving to ban its sale as of Sept. 30, citing an “imminent hazard to public safety.” The DEA in August announced it would make kratom a Schedule 1 drug -- the same as heroin, LSD, marijuana, and ecstasy. The decision was delayed after members of Congress urged the DEA to delay the ban and give the public a chance to comment. The DEA has withdrawn its intent to make kratom a Schedule 1 drug and established a public comment period through Dec. 1, 2018 according to a preliminary document available on the Federal Register website.

7.5-Kratom and the States

The DEA has yet to publish a final decision and the future status of kratom remains unknown. However, the current legality of kratom remains a gray area for many people. Kratom is currently legal in the United States but there are several states who have banned kratom making its use illegal.

According to <https://www.kratomnews.org/kratom-legal-status-map/> (October 2018) kratom is illegal in Alabama, Arkansas, Indiana, Ohio, Rhode Island, Tennessee, Vermont, Washington DC, and Wisconsin. It is also banned in Florida Sarasota county, Jerseyville (Illinois) and Denver (Colorado).

Some of the states’ rules have added to the confusion. The Indiana House of Representatives passed a bill that added the alkaloids mitragynine and 7-hydroxymitragynine to the list of Controlled Substances in that state. This law passed in 2012 made them the first state to try and control the use of Kratom. However, because Kratom is a natural plant as opposed to a synthetic substance, this law only prevents the alkaloids from being sold in synthetic formulations. As such, the Kratom plant has not been banned and is still legal in the state of Indiana.

7.6-Kratom in Other Countries

Kratom is not legal in Australia, Finland, Malaysia, Myanmar and Thailand. Kratom was used in Thailand for centuries but is now banned. When the Thai government started levying taxes from users and shops involved in the opium trade many users switched to kratom to manage their withdrawal symptoms.

8-Scheduling Recommendations

House Resolution 177 requests that the Louisiana Department of Health study the scheduling of Kratom and provide recommendations to the House Committee on Administration of Criminal Justice. This report has highlighted that few conclusive scientific studies have shed light on the physiologic effects, addictiveness, or risk to human health presented by kratom. Kratom—specifically the mitragynine alkaloid produced in the plant’s leaves—appears to have similar properties to opiates: it acts through the μ -opioid receptor, it’s observed physiologic effects are similar to those of other opiates, and it appears to similar addictiveness and withdrawal symptoms, albeit milder than more potent opiates. The FDA, under Commissioner Scott Gottlieb, has recommended that the DEA classify kratom as a Schedule I substance, arguing it exhibits a high abuse potential and has no accepted medical use. As noted above, the DEA had previously taken the action of banning kratom, only to reverse itself under pressure from advocates who argued the decision was made without adequate evidence to support banning. In the interim, eight states, three municipalities, and the District of Columbia have made kratom illegal in their jurisdictions.

LDH and state and local partners are not able to accurately estimate the prevalence of kratom use in Louisiana. According to the LEEDS database, no severe kratom-related events have been reported yet. Nevertheless, mounting evidence does indicate that kratom use could present a public health risk. As presented in this report, kratom production appears to lack quality control measures typically required of both medications and supplements, the product’s potency varies dramatically across formulations and producers, and the recent Salmonella outbreak highlights the potential for contamination with other potentially harmful substances and/or infectious agents. Additionally, kratom/mitragynine exhibits properties similar to other schedule I substances like lysergic acid diethylamide (LSD) and opiates like heroin, both of which have a high potential for abuse. Kratom currently has no accepted medical uses. Therefore, the Louisiana Department of Health recommends that kratom be banned from general consumption in the state, with exceptions made only in the context of well-designed scientific studies with appropriate oversight, data safety monitoring boards, and regulatory approval.

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