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Risk of death associated with kratom use compared to opioids

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ABSTRACT

Kratom use appears to be increasing across the United States, increasing attention to deaths in which kratom use was detected. Most such deaths have been ascribed to fentanyl, heroin, benzodiazepines, prescription opioids, cocaine and other causes (e.g., homicide, suicide and various preexisting diseases). Because kratom has certain opioid-like effects (e.g., pain relief), and is used by some people as a substitute for opioids for pain or addiction, kratom has been compared to "narcotic-like opioids" (e.g., morphine) with respect to risk of death despite evidence that its primary alkaloid, mitragynine, carries little of the signature respiratory depressing effects of morphine-like opioids. This commentary summarizes animal toxicology data, surveys and mortality data associated with opioids and kratom to provide a basis for estimating relative mortality risk. Population-level mortality estimates attributed to opioids as compared to kratom, and the per user mortality risks of opioids as compared to kratom are provided. By any of our assessments, it appears that the risk of overdose death is > 1000 times greater for opioids than for kratom. The limitations of the mortality risk estimate warrants caution in individuals with unknown factors such as use of other substances and medications, or other preexisting conditions. More research on kratom safety and risks is needed, as is regulation of commercial kratom products to ensure that consumers are informed by FDA labeling and that kratom products are not contaminated or adulterated with other substances.

1. Introduction and background

Kratom use appears to be increasing across the United State (US), drawing increased attention to deaths in which any level of kratom alkaloids (e.g., mitragynine (MG) and 7-hydroxyMG) has been detected in a decedent's plasma or any evidence suggesting that the decedent had consumed kratom. Mitragynine is primarily used as a marker for kratom exposure because it is the most prevalent alkaloid in kratom preparations whereas 7-hydroxyMG is generally at levels that are unlikely to contribute to pharmacological effects (Kruegel and Grundmann, 2018). The National Institute on Drug Abuse (NIDA, 2019a) provides the following summary on its "What is Kratom" web page:

> *There have been multiple reports of deaths in people who had ingested kratom, but most have involved other substances. A 2019 paper analyzing data from the National Poison Data System found that between 2011-2017 there were 11 deaths associated with kratom exposure. Nine of the 11 deaths reported in this study involved kratom plus other drugs and medicines, such as diphenhydramine (an antihistamine), alcohol, caffeine, benzodiazepines, fentanyl, and cocaine. Two deaths were reported following exposure from kratom alone with no other reported substances. In 2017, the FDA identified at least 44 deaths related to kratom, with at least one case investigated as possible use of pure kratom. The FDA reports note that many of the kratom-associated deaths appeared to have resulted from adulterated products 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 dietary supplements or dietary ingredients that were laced with other compounds that caused deaths. People should check with their health care providers about the safety of mixing kratom with other medicines.* [Italics added].

As implied by NIDA's summary, the actual contribution of kratom to these deaths is uncertain. Similarly, as discussed in a Centers for Disease Control and Prevention's (CDC) Morbidity and Mortality Weekly Report (MMWR) of 91 deaths that medical examiners and coroners had listed

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as “kratom involved” most included evidence of fentanyl, heroin, benzodiazepines, prescription opioids, and/or cocaine (Gershman et al., 2019; Olsen et al., 2019). In the seven cases that did not list a drug other than kratom as being detected, the authors noted that exposure to other drugs could not be ruled out due to inconsistencies in testing by medical examiners. The MMWR report drew no conclusion about the potential contribution of kratom to any of the deaths beyond stating that some level of exposure had occurred. The high variability of mitragynine levels ranging from 5.6–29,000 ng/mL detected in deaths associated with kratom exposure furthermore questions the association between mitragynine levels and toxicity (Papsun et al., 2019). Nonetheless, media headlines include phrases such as “kratom-linked” deaths, “kratom overdose deaths”, and “kratom deaths” (see e.g., Galvin, 2019; Kaur, 2019; Miller, 2019).

In fact, while the contribution of kratom to death in some cases cannot be ruled out, there has yet to be an overdose death from kratom alone in either the US or South East Asia where heavy kratom use is common (Prozialeck et al., 2019). This is consistent with pharmacologic studies and epidemiological investigations in Southeast Asia of kratom, which indicate that, in contrast to morphine-like opioids, kratom fails to produce life-threatening respiratory depression and generally is not associated with the personal and societal impairment associated with morphine-like opioids (Prozialeck et al., 2019; Singh et al., 2017; Veltri and Grundmann, 2019). This is likely because MG and 7-hydroxyMG function as partial agonists with respect to respiratory depressant effects due to their G-protein biased signaling mechanism of action (Kruegel et al., 2016; Kruegel and Grundmann, 2018; Váradi et al., 2016).

Animal studies that have attempted to determine the lethal dose of kratom have also failed to document acute overdose deaths with similar symptoms to morphine. Rather they have found that at dose equivalents of hundreds or more times the typical human dose range, some animals die over days or weeks due to a variety of causes unrelated to respiratory depression (Henningfield et al., 2018a; Prozialeck et al., 2019). For example, a study in which 100 mg/kg MG, p.o. administered to rats for 28 days produced only an increase in liver weight (Sabetghadam et al., 2013). No evidence of toxicity was found at doses as high as 920 mg/kg MG in dogs (Macko et al., 1972), or as high as 807 mg/kg MG in rats (Macko et al., 1972). Studies in rats reported lethal effects of 200 mg/kg total alkaloid extract of *M. speciosa* given intragastrically (Azizi et al., 2010; Janchawee et al., 2007); however, respiratory depression was not observed.

2. Surveillance data and user estimates can inform relative mortality risk

There is no nationally projectable survey for estimating the number of kratom consumers in the U.S.; however, it appears plausible that there are presently approximately 10–16 million or more current, regular kratom users in the US.[1] This suggests that there may be 48 million or more kratom exposures per month or 576 million per year over the past 1–2 years, which in turn suggests a very low rate of serious adverse events and deaths involving kratom.

Four internet surveys of > 20,000 kratom users, > 20,000 comments to the Drug Enforcement Administration (DEA), and a survey of > 500 people in treatment for opioid use disorder indicate that some fraction of kratom consumers are using kratom as an alternative to opioids (Coe et al., 2019; Grundmann, 2017a, 2017b; Henningfield et al., 2018a; Smith and Lawson, 2017). The opioids had been used for self-treating pain or addiction, and a prevailing motivator is the user's assumption that kratom carries far less risk of overdose death. This is consistent with opinions of many kratom experts in the US (Grundmann et al., 2018; Swogger and Walsh, 2018; Henningfield et al., 2018a, 2018b), as well as in South East Asia where kratom use is very common by itself and in place of opioids (Prozialeck et al., 2019).

In the context of the US opioid epidemic in which 46,600 opioid-attributed deaths were estimated by the CDC in 2017 (CDC, 2018), and which has been rapidly escalating for more than a decade (Jalal et al., 2018), it is important to provide some basis for estimating the relative risk of kratom-associated deaths as compared to morphine-like opioids. Some insight can be provided by a comparison of the numbers of deaths attributed to opioids with the numbers that have been reported as possibly involving kratom by the Food and Drug Administration (FDA) and NIDA. Two approaches are presented in Tables 1 and 2.

Table 1 provides a comparison of deaths attributed to opioids (primarily fentanyl, heroin, and prescription opioids) in the US in 2017, with various estimates of deaths that have been reported by the FDA as “associated with” kratom. The table includes the 43[2] kratom-associated deaths reported by FDA from the years 2011 to 2017, as well as an estimate that excludes deaths in which other causes of death were established as more likely than kratom, and an estimate of deaths from 2016 and 2017 in the US only to provide a more comparable basis to opioid deaths that are based on 2017 data.

Table 2 provides comparisons of death rates and relative risks per estimated number of kratom users and nonmedical opioid users.

Because all currently available information about the kratom user population comes from online or small sample surveys, the actual number of kratom users may vary considerably from the estimated approximately 16 million. However, the current number is the best and most conservative estimate for the US.

In all cases of kratom-associated, kratom-involved, kratom-positive, or kratom-reported cases the actual substance reported was the indole alkaloid, MG. In some cases, the substance was semi-quantified while in others it was simply reported as positive assuming the presence of kratom extract. In still other cases, the substance was assumed based on reports of use from family members. However, there is currently no correlation between MG blood levels and observed behavioral, adverse, or lethal effects. It is therefore unclear whether MG serves as a good indicator for reporting kratom intoxication and especially a kratom fatality. Some animal in vitro and in vivo experiments indicate that the structural analogue 7-hydroxy-MG may have a stronger affinity for the opioid receptor and pose a higher mortality risk. There are also initial studies showing that MG is metabolized to 7-hydroxy-MG by the liver; thus, the degree of potential toxicity may be limited and subject to interindividual metabolic variability (Kamble et al., 2019; Avery et al., 2019; Kruegel et al., 2019). As discussed by Kruegel et al. (2019), the processes mediating the metabolism of MG to 7-hydroxy-MG and the neuropharmacology of these substances may help explain the new findings related to mitragynine and the more favorable safety profile as compared to other substances that have morphine-like opioid receptor agonist activity.

3. Conclusions

Kratom is not without risk, but the risk estimates as calculated by any of the approaches used, relative to opioids, suggest that morphine-like opioids carry an overdose risk of a thousand or more times greater than kratom. This conclusion has the limitation that some kratom users

[1] The American Kratom Association surveyed export data from several Indonesian kratom grower's commercial export associations that document an average of 1.950 metric tons of kratom are exported on a monthly basis to the U.S. Based on an estimated daily 4–6 g/day per consumer, this yields a potential range 10.83 million–16.25 million kratom consumers. This should be considered a very rough estimate that does not account for heavy kratom users or the number of light non-daily users, which surveys suggest represent the majority of current kratom users. See http://www.americankratom.org/images/Kratom_Population_2019.pdf.

[2] Although FDA released 44 reports of kratom associated deaths, at least one case was reported twice as ID Nos. 14449343 and 14254346.

Table 1
Deaths associated with kratom and opioids estimated for 2017.

Drug class	Number of associated deaths estimated to have occurred in 2017	Past year use	Number of deaths in the (US) in 2017: ratio of opioids to kratom
Any morphine-like opioid including, licit and illicit fentanyl, heroin and oxycodone	47,600[a]	1.7 million suffering from OUD 652,000 suffering from heroin use disorder (not mutually exclusive)[b] 11,401,000 past year heroin use or pain reliever misuse [c,d]	
Prescription opioids	17,029[c,e, f, g]		
Kratom	6	10.83 million–16.25 million (see basis in footnote 1, *supra*)	7933 to 1
		Compared to prescription opioids	2838 to 1
General population	2.7 million deaths in the US	327 million US population	

[a] CDC, 2018, *supra*.
[b] NIDA, 2019c, *supra*.
[c] Substance Abuse and Mental Health Services Administration (SAMHSA, National Survey on Drug Use and Health (NSDUH), Data Tables, 2017.
[d] Does not include use with prescription and under guidance from a healthcare professional.
[e] NIDA, 2019b, *supra*.
[f] See also Sullum, 2019, *supra, stating that* 68% of prescription opioid overdose deaths also involved heroin, fentanyl, cocaine, barbiturates, benzodiazepines, or alcohol.
[g] As discussed by Scholten and Henningfield (2016a, 2016b), properly prescribed opioids carry a low risk of overdose or abuse, but prescription opioid associated reports typically include people who were not prescribed or who obtained prescriptions without legitimate medical need. Further, as discussed by Sullum, other substances (licit and illicit) appear to be strong drivers of overdose attributed to prescription opioids.

Table 2
Death rate and relative risks per estimated number of kratom users and nonmedical opioid users.

Drug class	Number of deaths "associated with kratom by the in FDA in 2017"	Use in past year	Death rate for past year use	Risk relative to kratom use
Kratom (estimate avg. 4 g/day/user)	6[a] (2017)	16,250,254[b]	0.000000369	1
Kratom (estimate avg. 6 g/day/user)	6[c] (2017)	10,833,502[d]	0.000000554	1
Any opioid	47,600[e] (2017)	11,401,000[f]	0.0042	11,382.1:1
Heroin	15,482[g] (2017)	324,000[h]	0.048	130,081.3:1

[a] Revised from the 44 deaths listed by FDA (2017) based on duplication of decadent ID No. 14449343 under ID No. 14254346.
[b] Based on American Kratom Association kratom tonnage import data and an estimated daily 4 g/day user base.
[c] Revised from the 44 deaths listed by FDA (2017) based on duplication of decedent ID No. 14449343 under ID No. 14254346.
[d] Based on kratom tonnage import data and an estimated daily 6 g/day user base.
[e] CDC, 2018, *supra*.
[f] Substance Abuse and Mental Health Services Administration (SAMHSA) (2017), Center for Behavioral Health Statistics and Quality, 2018.
[g] NIDA, 2019b, supra.
[h] Heroin users who did not use other opioids as described in SAMHSA, 2017, *supra*.

inherently carry or assume factors that might greatly increase the risk of kratom-associated mortality, e.g., use in combination with opioids, sedatives, alcohol or other drugs, or some preexisting disease states that may make kratom use especially risky. The fact that the causes of deaths that were associated with kratom use varied widely and included liver disease, homicide, suicide, trauma, and overdose with clearly lethal levels of other drugs (Babin, 2018; FDA, 2017; Henningfield et al., 2018b), cannot form the basis for concluding that co-existing conditions make kratom use more or less risky compared to opioids.

More studies of kratom safety are needed. As kratom use continues to increase, it is likely that among the 2,813,503 total US deaths per year (Kochanek et al., 2019), an increasing number will be cases in which kratom use was suspected or detected without determination or consideration of the potential involvement of other licit and/or illicit drug(s), in part due to inadequate postmortem toxicology data and testing protocols (Olsen et al., 2019; Gershman et al., 2019). While toxicology data in humans needs to be further explored, initial data indicate that long-term kratom use in traditional settings does not result in changes in several biochemical parameters related to safety (Singh et al., 2018). In addition, as is the case with many other dietary and herbal supplements, it is possible that adverse effects may result from interactions of kratom with other herbs as well as with medicines. Further studies will be important to guide labeling and consumer information. Of particular importance is a major nationally projectable survey that would provide a basis for estimating the number of past year and past month kratom users, amount of use, mode or type of kratom use, reasons for use, association with illness and other drug and substance use, and the extent and geographic distribution of people using kratom in place of opioids who might be at risk of relapse to opioid use if kratom was banned at the local, state or federal level. Because many deaths possibly involving kratom appear to have also involved opioids and other drugs that are known to carry a high risk of overdose death, a regulatory approach that establishes standards for kratom product purity, packaging, labeling, and alkaloid content is urgently needed to reduce the risks for persons who purchase lawfully marketed products. In this context, it is promising that four states have passed kratom consumer protection laws setting standards for kratom purity, labeling, minimum age of purchase, requiring registration and will include oversight. Legislators in other states are developing similar proposals (American Kratom Association, 2019).

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References

American Kratom Association, 2019. Nevada Governor Sisolak sign Kratom Consumer Protection Act – Nevada is now the 4th state to protect kratom consumers. https://www.americankratom.org/update.html, Accessed date: 30 August 2019.

Avery, B.A., Boddu, S.P., Sharma, A., Furr, E.B., Leon, F., Cutler, S.J., McCurdy, C.R., 2019. Comparative pharmacokinetics of mitragynine after oral administration of Mitragyna speciosa (Kratom) leaf extracts in rats. Planta Med. 85 (4), 340–346.

Azizi, J., Ismail, S., Mordi, M.N., Ramanathan, S., Said, M.I.M., Mansor, S.M., 2010. In vitro and in vivo effects of three different Mitragyna speciosa Korth leaf extracts on phase II drug metabolizing enzymes—glutathione transferases (GSTs). Molecules 15 (1), 432–441.

Babin, J., 2018. FDA fails to follow the science on Kratom. American Kratom Association. https://docs.wixstatic.com/ugd/9ba5da_54f08e1805c34c108ad7199481507d88.pdf, Accessed date: 30 April 2019.

Centers for Disease Control and Prevention (CDC) (2018) Drug overdose deaths at https://www.cdc.gov/drugoverdose/data/statedeaths.html (Accessed on August 4, 2019).

Center for Behavioral Health Statistics and Quality, 2018. 2017 National Survey on Drug Use and Health: Detailed Tables. In: Substance Abuse and Mental Health Services Administration. MD, Rockville.

Coe, M.A., Pillitteri, J.L., Sembower, M.A., Gerlach, K., Henningfield, J.E., 2019. Kratom as a substitute for opioids: results from an online survey. Drug Alcohol Depend. 202, 24–32.

Food and Drug Administration (2017) Basis for the Recommendations to Control Mitragynine and 7-Hydroxymitragynine in Schedule I of the Controlled Substances Act. https://www.documentcloud.org/documents/5031552-HHS-kratom-letter.html (Accessed on May 1, 2019).

Galvin, G. (2019). CDC Study Shows Kratom-Linked Overdose Deaths. U.S. News & World Reports. https://www.usnews.com/news/health-news/articles/2019-04-11/kratom-linked-overdose-deaths-examined-in-cdc-study. (Accessed on April 30th, 2019).

Gershman, K., Timm, K., Frank, M., Lampi, L., Melamed, J., Gerona, R., Monte, A.A., 2019. Deaths in Colorado attributed to Kratom. New Eng. J. Med. 380 (1), 97–98.

Grundmann, O., 2017a. Patterns of Kratom use and health impact in the US-results from an online survey. Drug Alcohol Depend. 176, 63–70.

Grundmann, O., 2017b. Patterns of Kratom use and health impact in the US—results from an online survey. Drug Alcohol Depend. 176, 63–70.

Grundmann, O., Brown, P.N., Henningfield, J., Swogger, M., Walsh, Z., 2018. The therapeutic potential of kratom. Addiction 113 (10), 1951–1953.

Henningfield, J.E., Fant, R.V., Wang, D.W., 2018a. The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. Psychopharmacology 235 (2), 573–589.

Henningfield, J., Babin, J., Griffiths, R., Boyer, E., Grundmann, O., Brown, P., Hemby, S., Garcia-Romeu, A., McCurdy, C., Raffa, R., Walsh, Z., Swogger, M., 2018b. Analysis of FDA's October 17, 2017 "Basis for the recommendations to control mitragynine and 7-hydroxymitragynine in Schedule I of the Controlled Substances Act.". https://www.americankratom.org/images/file/Scientists-Response-toFDA-Kratom-8FA–28-Nov-2018-FINAL.pdf, Accessed date: 30 April 2019.

Jalal, H., Buchanich, J.M., Roberts, M.S., Balmert, L.C., Zhang, K., Burke, D.S., 2018. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. Science 361 (6408), eaau1184.

Janchawee, B., Keawpradub, N., Chittrakarn, S., Prasettho, S., Wararatananurak, P., Sawangjareon, K., 2007. A high-performance liquid chromatographic method for determination of mitragynine in serum and its application to a pharmacokinetic study in rats. Biomed. Chromatogr. 21 (2), 176–183.

Kamble, S.H., Sharma, A., King, T.I., León, F., McCurdy, C.R., Avery, B.A., 2019. Metabolite profiling and identification of enzymes responsible for the metabolism of mitragynine, the major alkaloid of Mitragyna speciosa (kratom). Xenobiotica 49 (11), 1279–1288.

Kaur, H., 2019. More Deaths Have Been Associated With Kratom Than Previously Known. CDC study finds, CNN. https://www.cnn.com/2019/04/12/health/kratom-deaths-cdc-study/index.html, Accessed date: 9 September 2019.

Kochanek, K.D., Murphy, S.L., Xu, J.Q., Arias, E., 2019. Deaths: Final data for 2017. no 9 In: National Vital Statistics Reports. 68 MD: National Center for Health Statistics., Hyattsville.

Kruegel, A.C., Grundmann, O., 2018. The medicinal chemistry and neuropharmacology of kratom: a preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. Neuropharmacology 134, 108–120.

Kruegel, A.C., Gassaway, M.M., Kapoor, A., Váradi, A., Majumdar, S., Filizola, M., Javitch, J.A., Sames, D., 2016. Synthetic and receptor signaling explorations of the Mitragyna alkaloids: mitragynine as an atypical molecular framework for opioid receptor modulators. J. Am. Chem. Soc. 138 (21), 6754–6764.

Kruegel, A.C., Uprety, R., Grinnell, S.G., Langreck, C., Pekarskaya, E.A., Le Rouzic, V., Ansonoff, M., Gassaway, M.M., Pintar, J.E., Pasternak, G.W., Javitch, J.A., Majumdar, S., Sames, D., 2019. 7-Hydroxymitragynine is an active metabolite of mitragynine and a key mediator of its analgesic effects. ACS Cent. Sci. 5 (6), 992–1001.

Macko, E., Weisbach, J.A., Douglas, B., 1972. Some observations on the pharmacology of mitragynine. Arch. Int. Pharmacodyn. Ther. 198 (1), 145.

Miller, R. (2019) Herbal drug kratom linked to almost 100 overdose deaths, CDC says. https://www.usatoday.com/story/news/health/2019/04/11/kratom-herbal-drug-linked-overdose-deaths-cdc-says/3441560002/. (Accessed on April 30th, 2019).

National Institute on Drug Abuse (NIDA), 2019a. What Is Kratom? Drug Facts. https://www.drugabuse.gov/publications/drugfacts/kratom, Accessed date: 4 September 2019.

National Institute on Drug Abuse (NIDA), 2019b. Overdose death rates (revised January, 2019). https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates, Accessed date: 4 September 2019.

National Institute on Drug Abuse (NIDA), 2019c. Opioid overdose crisis (revised January, 2019). https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis, Accessed date: 4 September 2019.

Olsen, E.O., O'Donnell, J., Mattson, C.L., Schier, J.G., Wilson, N., 2019. *Notes from the Field:* unintentional drug overdose deaths with Kratom detected — 27 states, July 2016–December 2017. Morb. Mortal. Wkly Rep. 68, 326–327.

Papsun, D.M., Chan-Hosokawa, A., Friederich, L., Brower, J., Graf, K., and Logan, B. (2019). The trouble with kratom: analytical and interpretative issues involving mitragynine, J. Anal. Toxicol., Published online August 19, 2019 at doi:https://doi.org/10.1093/jat/bkz064.

Prozialeck, W., Avery, B., Boyer, E., Grundmann, O., Henningfield, J., Krueger, A., McMahon, L., McCurdy, C., Swogger, M., Veltri, C., Singh, D., 2019. Kratom policy: the challenge of balancing therapeutic potential with public safety. Int. J. Drug Pol. 70, 70–77.

Sabetghadam, A., Ramanathan, S., Sasidharan, S., Mansor, S.M., 2013. Subchronic exposure to mitragynine, the principal alkaloid of Mitragyna speciosa, in rats. J. Ethnopharmacol. 146 (3), 815–823.

Scholten, W. and Henningfield, J.E. (2016a) Negative outcomes of unbalanced opioid policy supported by clinicians, politicians, and the media. J. Pain Palliative Care Pharmacother. 2016;30(1):4–12.

Scholten, W., Henningfield, J.E., 2016b. Negative outcomes of unbalanced opioid policy supported by clinicians, politicians, and the media. Letter of response to Kolodny. J. Pain Palliative Care Pharmacother. 30 (4), 332–334.

Singh, D., Narayanan, S., Vicknasingam, B., Corazza, O., Santacroce, R., Roman-Urrestarazu, A., 2017. Changing trends in the use of kratom (Mitragyna speciosa) in Southeast Asia. Hum. Psychopharmacol. 32 (3). https://doi.org/10.1002/hup.2582. Epub.

Singh, D., Muller, C.P., Murugaiyah, V., Hamid, S.B.S., Vicknasingam, B.K., Avery, B., Chear, N.J.Y., Mansor, S.M., 2018. Evaluating the hematological and clinical-chemistry parameters of kratom (Mitragyna speciosa) users in Malaysia. J. Ethnopharmacol. 214, 197–206.

Smith, K.E., Lawson, T., 2017. Prevalence and motivations for kratom use in a sample of substance users enrolled in a residential treatment program. Drug Alcohol Depend. 180, 340–348.

Substance Abuse and Mental Health Services Administration (SAMHSA), 2017. National survey on drug use and health (NSDUH) 2017 detailed tables. https://www.samhsa.gov/data/report/2017-nsduh-detailed-tables, Accessed date: 4 September 2019.

Sullum, J., 2019. New Survey Data Confirm That Opioid Deaths Do Not Correlate With Pain Pill Abuse or Addiction Rates – Nonmedical Use of Prescription Analgesics Did Not Become More Common, But It Did Become More Dangerous. Reason.com. https://reason.com/2019/08/21/new-survey-data-confirm-that-opioid-deaths-do-not-correlate-with-pain-pill-abuse-or-addiction-rates/, Accessed date: 4 September 2019.

Swogger, M.T., Walsh, Z., 2018. Kratom use and mental health: a systematic review. Drug Alcohol Depend. 183, 134–140.

Váradi, A., Marrone, G.F., Palmer, T.C., Narayan, A., Szabó, M.R., Le Rouzic, V., Grinnell, S.G., Subrath, J.J., Warner, E., Kalra, S., Hunkele, A., Pagirsky, J., Eans, S.O., Medina, J.M., Xu, J., Pan, Y.X., Borics, A., Pasternak, G.W., McLaughlin, J.P., Majumdar, S., 2016. Mitragynine/corynantheidine pseudoindoxyls as opioid analgesics with mu agonism and delta antagonism, which do not recruit β-arrestin-2. J. Med. Chem. 59 (18), 8381–8397.

Veltri, C., Grundmann, O., 2019. Current perspectives on the impact of Kratom use. Subs. Abuse Rehabil. https://doi.org/10.2147/SAR.S16426.