

# *Mitragyna speciosa* as a Potential Substitute Therapy in Opioid Dependence: A Case Report

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## ABSTRACT

### ARTICLE HISTORY

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Preclinical data have consistently suggested the pharmaceutical potential of kratom (*Mitragyna speciosa*), including as a substitute therapy in opioid dependence. In this case report, we present a case of a man with a long history of kratom use to help him cope with his opiate withdrawals while abstaining from illicit drug use. This is the first published detailed case report highlighting the potential use of kratom to aid opioid dependence encountered in the clinical setting. Our article is also supported by literature review with regards to kratom's safety profile and pharmacological potential.

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## INTRODUCTION

Polysubstance abuse and opioid dependence are burgeoning issues stereotypically affecting the youths. They are closely linked to social ill with spurring juvenile crimes, hence risk public security due to the violent and erratic behavior derived from the psychostimulants' effects (Salas-Wright et al., 2017).

Clinical management of individuals with polysubstance abuse, addiction and dependence is intricately challenging as the program success highly depends on the degree of self-awareness, their personal drive and willingness to quit (Castine et al., 2019; Kennedy & Gregoire, 2009). Pharmacological therapy may help to an extent and to date, methadone is the most feasible and the cheapest mode of substitution therapy adopted by the Malaysian government as part of the harm reduction policy to curb opioid dependence in the community (Frank, 2020). Methadone is a synthetic opioid agonist with affinity towards the endogenous mu-opioid receptor with the preferential activation of  $\beta$ -arrestin over the G-proteins, hence relieving opioid withdrawal symptoms (Kapoor et al., 2020). The side effects, even were mild and somatic, might be intolerable to some, and this include excessive sweating, constipation and dry mouth (Haber et al., 2017). In such cases, therapy with other substitute therapy may be prescribed, such as suboxone or buprenorphine, often at a much higher cost.

Kratom or *Mitragyna speciosa* is a plant homogenous to the Southeast Asia with average range of the tree height is between 13-52 feet (Khalid et al., 2021) (Figure 1). It has dark green leaves and can grow up to 7 inches long and 4 inches wide (Figure 2).



Figure 1. Kratom (*Mitragyna speciosa*) tree.



Figure 2. Kratom (*Mitragyna speciosa*) leaves.

Recent years have witnessed promising results with regards to kratom potential in mitigating opiate dependence (Coe et al., 2019; Wilson et al., 2021; Wilson et al., 2020). Kratom continues to garner attention in view of its prolific potential. Small-scale clinical studies have attempted to establish the pharmacokinetic, safety profile and potential clinical use of kratom in humans (Metastasio et al., 2020; Vicknasingam et al., 2020; White, 2018). However, due to local and international binding legislation, extensive trials were often dissuaded and not given enough priority. In this case report, we present a case of a man with opioid dependency who successfully abstained from illicit drug use through self-administration of kratom. This is the first case of its kind highlighting the potential use of kratom to aid opioid dependence encountered in the clinical setting.

## METHOD

Data collection was performed through a single session of a one-to-one interview with the patient in May 2021. The session took 55 to 60 minutes to complete and was audio-recorded with written consent to ensure verbatim transcription.

Literature review was performed through specified keywords search using Boolean operators: 'kratom' OR 'ketum' AND 'opioioid' OR 'opiate' AND 'dependence' OR 'withdrawal' from both Medline and Google Scholar databases for articles published from the year 2000 to date.

## RESULTS

The case describes a man in his early 50s from northwest Peninsular Malaysia. His first involvement with illicit drug use began at the age of 24 in the year 1994 due to peer influence and environmental pressure. He was exposed to both heroin and cannabis, habitually taken for recreational purposes. He was an intravenous drug user (IVDU), injecting heroin 3-4 times per month, and cannabis was regularly smoked in cigarettes. His typical withdrawal symptoms from heroin include lethargy, chills, feeling aloof and detached from the surroundings. Over time, he developed tolerance, requiring more frequent injection. Despite so, since supply was readily available through peers, it did not affect his social functioning. On the other hand, smoking cannabis was habitual, and he was not dependent on it.

He decided to turn over a new leaf after he was eventually caught and detained for drug abuse four years later and spent some time in jail. Soon after his release, he was determined to stop misusing illicit drugs, hence replacing heroin with kratom to treat his heroin addiction. His early kratom use in the year 2005 was in a powdered

form made from dried kratom leaves, taken 2 spoonfuls with mineral water, 3 times per day. Each dose would last him for 4 to 5 hours before withdrawal symptom sets in. He denied of tolerance symptoms and claimed to be on the same dose throughout the years.

There were no significant changes in experience since until the beginning of the year 2008, when he started taking kratom in beverage form (Figure 3) bought from the underground market, which he claimed to be more accessible.



**Figure 3. Kratom beverage commonly sold in single-use plastics.**

He took 1 to 2 cups in the morning and another 2 cups at night. However, he had begun making his own kratom beverage a little while later when supplies of kratom leaves were easier to get. He was able to get fresh kratom leaves sold at MYR 20 (less than \$5) for 1 kilogram, which lasted for 10 days. He claimed the same dosage was used throughout the years to reduce his opioid withdrawal symptoms and addiction. His kratom preparation was made pure, from boiling the leaves for two hours straight (leaving the water from full to half pot), giving it a mossy green color. The water was then filtered for impurities and sediments, and was kept cool before drinking. He was able to maintain his usual daily activities with these 3 cups of self-prepared kratom beverage daily, taken 1 cup every morning, afternoon, and night. Throughout his kratom use, he completely abstained from illicit drug use, including heroin.

His regular kratom use allows him to perform well at work. He has had a stable office job and had even received awards for excellent work performance throughout his career, twice. However, he had enrolled to the local methadone maintenance program in the year 2021 in his effort to transition his kratom use to methadone in view of the local legislation risk with kratom. His baseline haematological and biochemical data screened at the beginning of methadone programme showed mild liver derangements: Haemoglobin: 15.3 d/dL, urea: 3.1 mmol/L, creatinine: 72  $\mu$ mol/L, total protein: 88 g/L, albumin: 36 g/L, alkaline phosphatase:

117 U/L, aspartate aminotransferase: 270 U/L, alanine aminotransferase: 241 U/L. In comparison, he felt that methadone was technically easier to administer as it is in the liquid form. He was started on 30 mg daily dose, however, is currently still experiencing withdrawal symptoms from kratom, hence was still on dose titration. Methadone, according to him, causes incessant dry mouth, hence he needed to chew gums regularly and drink a lot of water.

Throughout his methadone program over the past two months, the withdrawal symptoms from kratom were described to be far worse than that experienced from heroin. Among the symptoms described from kratom withdrawal were crippling headache, body aches, chills, sweatiness, watery eyes, and loss of appetite. Furthermore, throughout the years of kratom use, he had also noticed the development of skin hyperpigmentation (Figure 4), dirty sclera, and dark circles under the eyes, which, according to him, were pathognomonic phenotypes associated with chronic kratom use.



**Figure 4. Skin hyperpigmentation is commonly associated with long term kratom use (red arrows).**

## DISCUSSION

Our case exemplifies kratom potential to aid opiate addiction and dependence. The use of kratom in Malaysia in early 2005 was popular as a powdered form. Fifty grams of the powder were sold at MYR5 (~\$1), whereas kratom as a beverage form was only introduced beginning the year 2008. However, various kratom concoctions admixed with harmful substances, such as cough syrup and ashes from the mosquito coils were fashioned to appeal the youngsters with more euphoric effects, eventually giving its notorious name to this day (Khalid et al., 2021).

Kratom has been traditionally used for a wide range of mild ailments, including diarrhea, fever, and pain (Meireles et al., 2019), attributable to the biologically active compounds found in its extract. The two main alkaloid extracts from kratom that are of great interest are the Mitragnynine (MG) and the 7-hydroxymitragnynine (7-HMG) that are known to have high affinity towards the mu-opioid receptors. Of the two, there are growing evidence of MG having anti-depressant, anti-nociceptive, anti-addiction, and anxiolytic effect (Meireles et al., 2019). Furthermore, repeated doses with MG were not found to result in opiate toxicity as seen with other opioids such as morphine. This could be explained by the absence of further receptor upregulation upon the saturation of substrate-receptor bindings, even with increased dosing (Kruegel et al., 2016; Váradi et al., 2016). Additionally, MG is generally regarded as safe as there were variations with regards to MG pharmacokinetics with the reported  $C_{max}$  of 423.68 ng/ml, 0.63 ug/ml, and 0.7 ug/ml at 20 mg/kg (de Moraes et al., 2009), 40 mg/kg (Janchawee et al., 2007), and 50 mg/kg (Parthasarathy et al., 2010) per oral dose with the corresponding  $T_{max}$  of 1.26 hours, 1.83 hours, and 4.50 hours, respectively. This reflects that the MG absorption is slow and minimal through oral administration.

In contrast, 7-HMG is known to exert greater binding affinity to mu-opioid receptor as compared to MG, hence increased the risk for addiction, dependence (Hemby et al., 2019 and tolerance to kratom (Matsumoto et al., 2008). Chronic exposure to 7-HMG was also associated with functional cognitive decline, including memory deficit and reduced capacity for new learning (Hemby et al., 2019). The presence of various alkaloids with diverse biological effects in kratom warrant caution as kratom beverage was harnessed from the leaves whole and there was no exact and consistent quantification of the different alkaloids present in the drink. Therefore, long term capricious use of kratom may result in undesirable effects that may eventually interrupt social functioning (Hassan et al., 2019; Hemby et al., 2019).

In our case, the patient used kratom to aid heroin withdrawal. The severity of heroin withdrawal is contingent upon many factors including the average intake, potency, and frequency of heroin use prior to the attempt to quit or scale back. The severity of the symptoms is commonly assessed through the Clinical Opioid Withdrawal Scale (COWS) (Wallace & Papp, 2017) in the clinical setting. In such cases, the standard medical procedure involves a thorough medical and psychiatric assessment, followed by a supervised medical detox program.

Following a long history of kratom use to aid heroin dependence, our patient eventually decided to enroll in our methadone program in view of the constrictive legislation with regards to kratom. According to available literatures, kratom withdrawals have been treated with buprenorphine-naloxone (Diep et al., 2018; Khazaeli et al., 2018; Weiss & Douglas, 2021), benzodiazepines (Sablaban & Gautam, 2020), and several other symptom-triggered drugs including naltrexone, dihydrocodeine, hydroxyzine (Stanciu et al., 2019) and others with reportedly better treatment response than methadone. Long term maintenance, however, needs to be strategically planned to prevent future relapse.

Scientific efforts to translate preclinical studies involving kratom use as a controlled medicine persistently lag due to legal restrictions and vague policy. Furthermore, there needs to be a consistent and reliable method to precisely extract the various compounds within the kratom to clearly distinguish and affirm its specific biological property. Additionally, the alkaloid contents in the kratom leaves differ according to the different stages of maturity and the tree ecotype (Brown et al., 2017).

Despite the limitation of our study methodology of a single descriptive case report, it was the first paper of its kind highlighting the potential of kratom as a substitute in the treatment of opioid dependence, despite the strong literature going against its clinical use due to the risk of addiction and other adverse health events (Corkery et al., 2019; Matson & Schenk, 2019; Palasamudramet al., 2019). We believe that judicial kratom use in clinical research should be encouraged under strict regulation and multiagency supervision to potentiate exploration of kratom as a pharmacological option not only for opioid addiction (Hemby et al., 2019), but also as anxiolytic (Hemby et al., 2019), treatment modality for chronic pain (Hemby et al., 2019), anti-cholesterol, and anti-diabetes medication (Brown et al., 2017).

## CONCLUSION

This case underscores the yet-to-be-explored kratom's potential to treat opioid dependence as substitution therapy other than methadone, in humans. However, given its foreseeable risk for abuse, proper monitoring and careful dose titration in humans should be pharmacologically tested and evaluated. Legislative planning and interdisciplinary consensus with regards to kratom use should be established to secure scientific breakthroughs that would benefit healthcare, at the same time taking public health and societal expectation into consideration.

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## CONFLICT OF INTEREST

The authors declare no competing interest.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was registered with the National Medical Research Register of the Ministry of Health Malaysia (NMRR-21-148-58441). Written consent was obtained from the patient for publication of the case history.

## REFERENCES

- Brown, P. N., Lund, J. A., & Murch, S. J. (2017, April 18). A botanical, phytochemical and ethnomedicinal review of the genus *Mitragyna* korth: Implications for products sold as kratom. *Journal of Ethnopharmacology*. Elsevier. <https://doi.org/10.1016/j.jep.2017.03.020>
- Castine, B. R., Albein-Urios, N., Lozano-Rojas, O., Martinez-Gonzalez, J. M., Hohwy, J., & Verdejo-Garcia, A. (2019). Self-awareness deficits associated with lower treatment motivation in cocaine addiction. *American Journal of Drug and Alcohol Abuse*, 45(1), 108–114. <https://doi.org/10.1080/00952990.2018.1511725>
- Coe, M. A., Pillitteri, J. L., Sembower, M. A., Gerlach, K. K., & Henningfield, J. E. (2019). Kratom as a substitute for opioids: Results from an online survey. *Drug and Alcohol Dependence*, 202, 24–32. <https://doi.org/10.1016/J.DRUGALCDEP.2019.05.005>
- Corkery, J. M., Streete, P., Claridge, H., Goodair, C., Papanti, D., Orsolini, L., ... Hendricks, A. (2019). Characteristics of deaths associated with kratom use. *Journal of Psychopharmacology*, 33(9), 1102–1123. <https://doi.org/10.1177/0269881119862530>
- de Moraes, N. V., Moretti, R. A. C., Furr, E. B., McCurdy, C. R., & Lanchote, V. L. (2009). Determination of mitragynine in rat plasma by LC-MS/MS: Application to pharmacokinetics. *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences*, 877(24), 2593–2597. <https://doi.org/10.1016/j.jchromb.2009.06.023>

- Diep, J., Chin, D. T., Gupta, S., Syed, F., Xiong, M., & Cheng, J. (2018). Kratom, an Emerging Drug of Abuse: A Case Report of Overdose and Management of Withdrawal. *A&A Practice*, *10*(8), 192–194. <https://doi.org/10.1213/xa.0000000000000658>
- Frank, D. (2020). Methadone maintenance treatment is swapping one drug for another, and that's why it works: Towards a treatment-based critique of the war on drugs. *International Journal of Drug Policy*, *83*, 102844. <https://doi.org/10.1016/j.drugpo.2020.102844>
- Haber, P. S., Elsayed, M., Espinoza, D., Lintzeris, N., Veillard, A. S., & Hallinan, R. (2017). Constipation and other common symptoms reported by women and men in methadone and buprenorphine maintenance treatment. *Drug and Alcohol Dependence*, *181*, 132–139. <https://doi.org/10.1016/j.drugalcdep.2017.09.024>
- Hassan, Z., Suhaimi, F. W., Ramanathan, S., Ling, K. H., Effendy, M. A., Müller, C. P., & Dringenberg, H. C. (2019). Mitragnynine (Kratom) impairs spatial learning and hippocampal synaptic transmission in rats. *Journal of Psychopharmacology*, *33*(7), 908–918. <https://doi.org/10.1177/0269881119844186>
- Hemby, S. E., McIntosh, S., Leon, F., Cutler, S. J., & McCurdy, C. R. (2019). Abuse liability and therapeutic potential of the *Mitragnyna speciosa* (kratom) alkaloids mitragnynine and 7-hydroxymitragnynine. *Addiction Biology*, *24*(5), 874–885. <https://doi.org/10.1111/adb.12639>
- Janchawee, B., Keawpradub, N., Chittrakarn, S., Prasettho, S., Wararatananurak, P., & Sawangjareon, K. (2007). A high-performance liquid chromatographic method for determination of mitragnynine in serum and its application to a pharmacokinetic study in rats. *Biomedical Chromatography*, *21*(2), 176–183. <https://doi.org/10.1002/bmc.731>
- Kapoor, A., Provasi, D., & Filizola, M. (2020). Atomic-level characterization of the methadone-stabilized active conformation of  $\mu$ -opioid receptor. *Molecular Pharmacology*, *98*(4), 475–486. <https://doi.org/10.1124/mol.119.119339>
- Kennedy, K., & Gregoire, T. K. (2009). Theories of motivation in addiction treatment: Testing the relationship of the transtheoretical model of change and self-determination theory. *Journal of Social Work Practice in the Addictions*, *9*(2), 163–183. <https://doi.org/10.1080/15332560902852052>
- Khalid, K., Ku Md Saad, S., Soelar, S. A., Mohamed Yusof, Z., & Warijo, O. (2021). Exploring adolescents' practice and perspective on the use and misuse of kratom in northwest Malaysia. *Journal of Ethnicity in Substance Abuse*. <https://doi.org/10.1080/15332640.2021.1906816>
- Khazaeli, A., Jerry, J. M., & Vazirian, M. (2018). Treatment of kratom withdrawal and addiction with buprenorphine. *Journal of Addiction Medicine*, *12*(6), 493–495. <https://doi.org/10.1097/ADM.0000000000000435>
- Kruegel, A. C., Gassaway, M. M., Kapoor, A., Váradi, A., Majumdar, S., Filizola, M., ... Sames, D. (2016). Synthetic and receptor signaling explorations of the mitragnyna alkaloids: Mitragnynine as an atypical molecular framework for opioid receptor modulators. *Journal of the American Chemical Society*, *138*(21), 6754–6764. <https://doi.org/10.1021/jacs.6b00360>
- Matson, M., & Schenk, N. (2019). Fatality of 33-Year-Old Man Involving Kratom Toxicity. *Journal of Forensic Sciences*, *64*(6), 1933–1935. <https://doi.org/10.1111/1556-4029.14082>
- Matsumoto, K., Takayama, H., Narita, M., Nakamura, A., Suzuki, M., Suzuki, T., ... Horie, S. (2008). MGM-9 [(E)-methyl 2-(3-ethyl-7a,12a-(epoxyethoxy)-9-fluoro-1,2,3,4,6,7,12,12b-octahydro-8-methoxyindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate], a derivative of the indole alkaloid mitragnynine: A novel dual-acting  $\mu$ - and  $\kappa$ -opioid agonist with potent a. *Neuropharmacology*, *55*(2), 154–165. <https://doi.org/10.1016/j.neuropharm.2008.05.003>
- Meireles, V., Rosado, T., Barroso, M., Soares, S., Gonçalves, J., Luís, Â., ... Gallardo, E. (2019). *Mitragnyna speciosa*: Clinical, Toxicological Aspects and Analysis in Biological and Non-Biological Samples. *Medicines*, *6*(1), 35. <https://doi.org/10.3390/medicines6010035>
- Metastasio, A., Prevete, E., Singh, D., Grundmann, O., Prozialeck, W. C., Veltri, C., ... Corazza, O. (2020). Can Kratom (*Mitragnyna speciosa*) Alleviate COVID-19 Pain? A Case Study. *Frontiers in Psychiatry*, *11*, 1298. <https://doi.org/10.3389/fpsy.2020.594816>
- Palasamudram Shekar, S., Rojas, E. E., D'Angelo, C. C., Gillenwater, S. R., & Martinez Galvis, N. P. (2019). Legally lethal kratom: A herbal supplement with overdose potential. *Journal of Psychoactive Drugs*, *51*(1), 28–30. <https://doi.org/10.1080/02791072.2018.1562591>
- Parthasarathy, S., Ramanathan, S., Ismail, S., Adenan, M. I., Mansor, S. M., & Murugaiyah, V. (2010). Determination of mitragnynine in plasma with solid-phase extraction and rapid HPLC-UV analysis, and its application to a pharmacokinetic study in rat. *Analytical*

- and *Bioanalytical Chemistry*, 397(5), 2023–2030. <https://doi.org/10.1007/s00216-010-3707-7>
- Sablabaan, I. M., & Gautam, M. (2020). The diagnosis of severe obsessions in the setting of kratom withdrawal and treatment with lorazepam: Case report. *Journal of Addictive Diseases*, 39(1), 138–139. <https://doi.org/10.1080/10550887.2020.1813357>
- Salas-Wright, C. P., Vaughn, M. G., & Reingle González, J. M. (2017). *Drug abuse and antisocial behavior : a biosocial life course approach*. Springer.
- Stanciu, C. N., Gnanasegaram, S. A., Ahmed, S., & Penders, T. (2019). Kratom withdrawal: A systematic review with case series. *Journal of Psychoactive Drugs*. Taylor & Francis. <https://doi.org/10.1080/02791072.2018.1562133>
- Váradi, A., Marrone, G. F., Palmer, T. C., Narayan, A., Szabó, M. R., Le Rouzic, V., ... Majumdar, S. (2016). Mitragynine/Corynantheidine Pseudoindoxyls As Opioid Analgesics with Mu Agonism and Delta Antagonism, Which Do Not Recruit  $\beta$ -Arrestin-2. *Journal of Medicinal Chemistry*, 59(18), 8381–8397. <https://doi.org/10.1021/acs.jmedchem.6b00748>
- Vicknasingam, B., Chooi, W. T., Rahim, A. A., Ramachandram, D., Singh, D., Ramanathan, S., ... Chawarski, M. C. (2020). Kratom and pain tolerance: a randomized, placebo-controlled, double-blind study. *Yale Journal of Biology and Medicine*, 93(2), 229–238. Retrieved from [/pmc/articles/PMC7309661/](https://pubmed.ncbi.nlm.nih.gov/37309661/)
- Wallace, M. S., & Papp, A. (2017). Opioid withdrawal. In *Challenging Cases and Complication Management in Pain Medicine* (pp. 15–20). StatPearls Publishing. [https://doi.org/10.1007/978-3-319-60072-7\\_3](https://doi.org/10.1007/978-3-319-60072-7_3)
- Weiss, S. T., & Douglas, H. E. (2021). Treatment of kratom withdrawal and dependence with buprenorphine/naloxone: A case series and systematic literature review. *Journal of Addiction Medicine*, 15(2), 167–172. <https://doi.org/10.1097/ADM.0000000000000721>
- White, C. M. (2018, March 1). Pharmacologic and clinical assessment of kratom. *American Journal of Health-System Pharmacy*. Oxford Academic. <https://doi.org/10.2146/ajhp161035>
- Wilson, L. L., Chakraborty, S., Eans, S. O., Cirino, T. J., Stacy, H. M., Simons, C. A., ... McLaughlin, J. P. (2021). Kratom alkaloids, natural and semi-synthetic, show less physical dependence and ameliorate opioid withdrawal. *Cellular and Molecular Neurobiology* 2021 41:5, 41(5), 1131–1143. <https://doi.org/10.1007/S10571-020-01034-7>
- Wilson, L. L., Harris, H. M., Eans, S. O., Brice-Tutt, A. C., Cirino, T. J., Stacy, H. M., ... McCurdy, C. R. (2020). Lyophilized Kratom Tea as a Therapeutic Option for Opioid Dependence. *Drug and Alcohol Dependence*, 216, 108310. <https://doi.org/10.1016/j.drugalcdep.2020.108310>