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Mitragyna speciosa: Opioid Addiction Treatment and Risk of Use

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Abstract: Kratom (*Mitragyna speciosa* (Korth.) Havil.) is a plant that originated from the rainforest in Southeast Asia, mainly grows in Thailand, Malaysia, and Indonesia. Kratom has been used traditionally as an herbal remedy for the treatment of various illnesses. Kratom gained notoriety due to its potential as an analgesic, opiate withdrawal treatment, anxiolytic, antidepressant, and antidiabetic with an unclear risk of addiction and toxicity fueled by a false sense of security due to its identity as a member of the coffee family. This article is a narrative review on kratom to highlight its pharmacological and toxicological properties, and the analytical method of Kratom, especially its potential as an opioid withdrawal therapy and its risk of abuse.

Keywords: kratom; kratom addiction; kratom toxicity; *Mitragyna speciosa*; mitragynine; 7-hydroxymitragynine

1. Introduction

Mitragyna speciosa (Korth.) Havil., commonly known as Kratom, ketum, or pudik is a species endogenous in Southeast Asia (Rech *et al*., 2015). Kratom has been used traditionally for various treatments, mainly for reducing fatigue, diarrhea, cough, chronic pain, and opium withdrawal. It can be chewed, smoked, swallowed as pills, or drunk by brewing (Ratsch, 2005).

Nowadays, with the widespread use of the internet, Kratom has become famous and exported to western countries as a treatment for chronic pain or self-medication for opium withdrawal. Sadly, this is also followed by abuse of Kratom, gaining notoriety as a recreational substance due to its opioid activity (Cinosi *et al*., 2015; Prozialeck *et al*., 2012; Raffa, 2014). Helped by a false sense of security due to the perception of "safe" and "natural" remedies, toxicity and death cases related to kratom are increasing year by year (Corkery *et al*., 2019). This leads to restriction and illegalization of Kratom in various countries (EMCDDA, 2012; Great Britain, 2016; Departement of Health, 2017). However, changes in its legal status have occurred in Thailand, Malaysia, and Indonesia (Yusof, 2019; Menteri Pertanian Republik Indonesia, 2020; Sattaburuth & Wannapiroon, 2021). Whether to be classified as a supplement or drug of abuse, kratom analysis demand is rising. Thus, a selective and sensitive method is needed to detect kratom within the sample whether using plant material and preparation for

sample identification or biological samples like urine and plasma for medical and forensic purposes.

Kratom's unique phytochemical composition made it have the potential to be used as both treatments for addiction and substance abuse. These properties made the judgment of kratom's legal status difficult. A better understanding of Kratom is needed to clarify the controversies regarding the risks and benefits of Kratom. Is Kratom a safe substance? What are the risks of Kratom consumption? And how do we detect Kratom and its metabolites? This review is trying to shed light on these questions. We include the botany and history of kratom, its components, pharmacology and toxicology, and analytical method development of Kratom and its products to offer a comprehensive insight regarding Kratom.

2. The Botany of Kratom

Kratom or Ketum or Purik, also known as *Mitragyna speciosa* (Korth.) Havil. is an evergreen tree that originated from the Southeast Asia rainforest, mainly growing in Thailand, Malaysia, Indonesia, and other surrounding countries (Rech *et al*., 2015). The plant is part of the Rubiaceae (coffee) family, mainly grows in a tropical and subtropical climate. Rubiaceae family is very diverse ranging from small herbs and vines to huge trees, with over 13,000 species. Some common traits of this family are opposite or whorled simple leaves, and interpetiolar stipules. The genus Mitragyna belongs to the Naucleeae tribe of the Cinchonoideae subfamily, which is characterized by congested inflorescence heads, flowers with fused ovaries, and indehiscent multiple fruits (Razafimandimbison & Bremer, 2001).

The species first described by the Dutch botanist, Pieter Willem Korthals, later transferred the species to another genus, Stephegyne. Other authors also transferred and renamed the species *Nauclea korthalsii* (Steudel, 1841), *Nauclea luzoniensis* (Blanco, 1845), *Nauclea speciosa* (Miquel 1856). In his revision of the tribe Naucleeae, Haviland (1897) transferred the species back into the genus Mitragyna and set the currently accepted species name as *Mitragyna speciosa* (Korth.) Havil. The genus Mitragyna are trees or shrubs with opposite leaves and keel-shaped stipules, sessile flowers, and heads are located at the end of side shoots (Raffa, 2014). Kratom tree could grow up to 25 m tall, and averaged around 3-4 m, with stem diameter up to 1 m. Kratom usually has a straight trunk with smooth and greyish outer bark, with elliptic leaves ranging around 14-20 cm long and 7-12 cm wide. Typically, the leaves bear 12-15 pairs of veins (Chua & Schmelzer, 2001).

Kratom is commonly grown and distributed in the Malesian floristic region, a phytogeographical region including the Malay Archipelago, New Guinea, and the Bismarck Archipelago which is based on shared flora distribution (Wikramanayake *et al*., 2002). In

Indonesia, Kratom can be found in South Kalimantan, Indonesia. Kratom is described as flood-tolerant and as pioneer species along abandoned river channels. This trait means Kratom can be utilized for ecological restoration in flood-prone areas (Nilus, 2011).

3. Kratom Use in Society

Kratom leaves have been used as traditional medicines in the various region in Southeast Asia (Assanangkornchai *et al*., 2007). The leaves can be chewed, smoked, made into pills, or brewed with hot water and served as tea (Ratsch, 2005). The leaves have been applied directly to wounds as a local anesthetic, and antihelminth. The leaves extracts are used to treat coughs, colds, diarrhea, diabetes, hypertension, malaria, general weakness, musculoskeletal pain, and opium substitute, as well as to increase stamina and sexual prowess (Suwanlert, 1975; Chua and Schmelzer, 2001; Assanangkornchai *et al*., 2007; Tanguay, 2011; Ahmad & Aziz, 2012; Neng *et al*., 2015; Papsun *et al*., 2019; Singh *et al*., 2019a). Due to its stimulant effect, Kratom is often consumed by local laborers to increase the work rate and reduce fatigue (Cinosi *et al*., 2015).

In modern society, Kratom has gained widespread usage in various countries. In Thailand and Malaysia, Kratom is one of the most commonly used recreational drugs due to its availability, the long tradition of usage, and perceived safety of use even though its dependence has been known and documented. The emergence of Kratom in Europe and the United States occurs around the 1980s and 1990s (Veltri & Grundmann, 2019). Nowadays the use, distribution, and formulation of Kratom have become available through the Internet and are known as analgesics among chronic pain individuals. Today Kratom became known as legal doping to increase athlete performance and also as a “legal” high substance and alternative to traditional opioids (Prozialeck *et al*., 2012; Raffa, 2014; Cinosi *et al*., 2015; Yusof, 2019).

Common motive for kratom consumption are either coping ($t_{87.09} = 3.544$, $p < 0.001$) and enhancement ($t_{114} = 2.180$, $p = 0.03$), with higher coping score correlate with higher daily dose of kratom consumption (Singh *et al*., 2019b). Some reasons included in these criteria are chronic pain, self-medication, opiate addiction, anxiety, and stress. Improving sexual performance also became one of the main enhancement motivations, with 85% (79/92) reporting improvement in sexual performance (Singh *et al*., 2019a). With the increasing popularity of Kratom, case of toxicity and deaths related to Kratom use also increased. The first known death occurred in 2008, and has been increasing ever since. From 156 deaths associated with Kratom, 27 deaths are where mitragynine was the sole drug implicated. Demographics of the victims are 80% male aged 17-64 years old (Corkery *et al*., 2019). During 18 months in 2016-2017, 152 deaths have been related to Kratom overdose in the United States (Olsen, 2019).

4. Physicochemical Profile of *Mitragyna speciose*

The study about kratom physicochemical properties has been done for more than 100 years. Since then, more than 70 individual alkaloids have been described along with a plethora of other secondary metabolites (Brown *et al*., 2017). The total alkaloid content in the leaves is around 0.5% to 1.5%. Mitragynine, the major alkaloid of Kratom is thought to be responsible for its opioid activity. Depending on its maturity state and environment, the mitragynine content can vary greatly from 12% to 66% of the total alkaloids content (Takayama, 2004; León *et al*., 2009; Brown *et al*., 2017). Commercial products labeled as kratom also show dramatic variation (Figure 1) (Kikura-Hanajiri *et al*., 2009; Mudge & Brown, 2016).

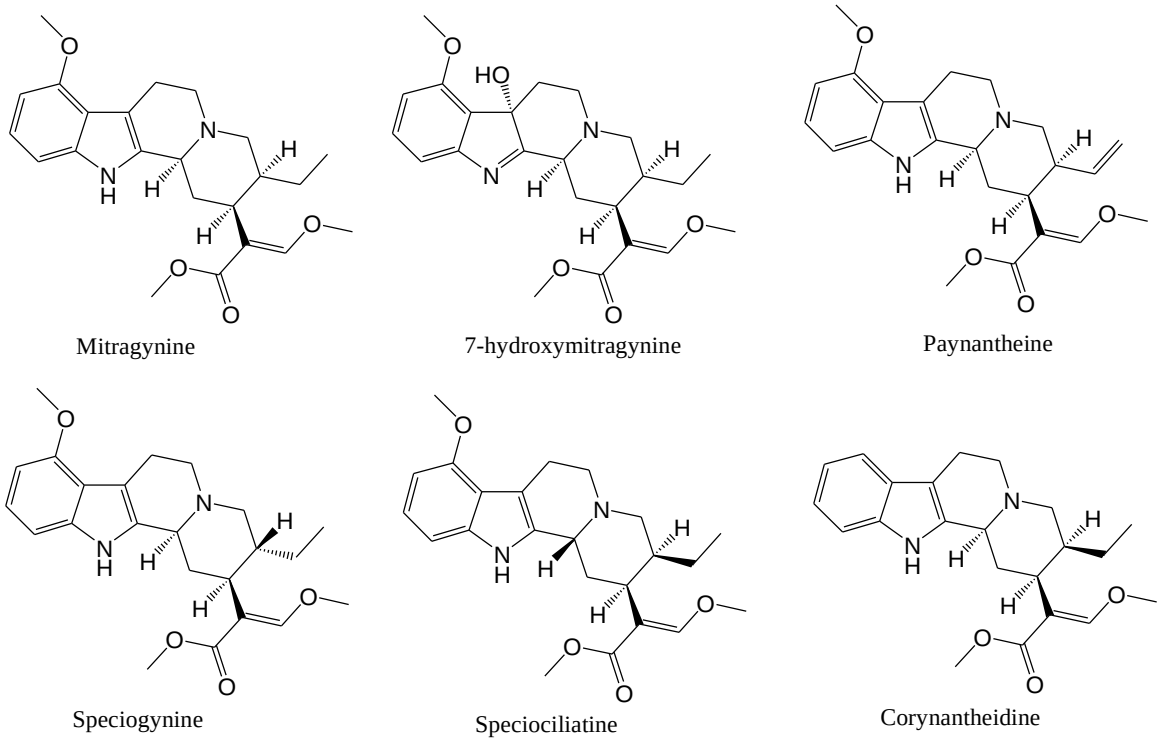

Figure 1. Structure of Mitragynine, the major alkaloid compound of Kratom, and its derivates.

Mitragynine is not the only major compound found in Kratom. Other prominent compounds found are mitragynine analogs: 7-hydroxymitragynine (7-HMG), speciogynine, paynantheine, and speciociliatine. A recent study shows that even though mitragynine is the more abundant substance, 7-hydroxymitragynine, which comprises around 2% of the total alkaloid content, is significantly more active, even superior to morphine. These alkaloids can be extracted from either methanolic extract or ethyl acetate extract, although the exact composition of the extract may vary (Kapp *et al*., 2011; Hassan *et al*., 2013).

Mitragynine is an indole alkaloid with 398.503 g/mol molecular weight , a weak base (pKa = 8.11 + 0.11), with LogP values of 1.70, LogD (pH 4) values of 0.78, and unstable at acidic environment. Mitragynine is not a substrate for P-glycoprotein and is permeated through the membrane by diffusion (Ramanathan *et al*., 2015; Ya *et al*., 2019).

Additional classes of secondary metabolite have been found and isolated in Kratom, including triterpenoids, flavonoids, and polyphenols. Ursolic acid and oleanolic acid were able to be isolated from root cultures of Kratom infected with *Agrobacterium rhizogenes* (Phongprueksapattana *et al*., 2008). Flavonoid compounds such as apigenin and its flavonol derivates such as quercetin have been isolated, including their respective glycosides. As for phenolic compounds, chlorogenic acid and caffeic acid were able to be isolated (Raffa, 2014).

5. Pharmacology and Toxicology of Kratom

5.1. Pharmacology of kratom

The pharmacology and toxicology of Kratom and its isolates have been discussed and reviewed extensively. Kratom effects are dose-dependent, where a small dose will induce a stimulant effect, while a higher dose will produce sedation and opioid effect (Jessica *et al*., 2011). The analgesic and opiate effect of Kratom has been associated with two alkaloid substances, mitragynine, and 7-hydroxymitragynine. The compounds aren't considered opioids by their organic structure, but due to their mechanism of action and their pharmacology effect. The two compounds are μ-opioid receptor agonists, with 7-HMG, the most potent opioid compound present showing a 13-fold higher opioid effect over morphine. The opioid effect on both the central nervous system and systemic effect can be inhibited by an opioid antagonist (Zarembo *et al*., 1974; Takayama *et al*., 2002; Matsumoto *et al*., 2004; Oberbarnscheidt & Miller, 2019). A study on the structure-activity relationship of mitragynine in tandem with in vitro radioligand binding assays and in vivo studies of mice also support this, with the addition that the negative and addictive effects are calculated to be less intense than morphine (Váradi *et al*., 2016).

Animal studies on kratom alkaloids in regards to psychological effects show that kratom can affect locomotor activity in a dose-dependent manner. Low dose (1mg/kg) shows an increase in locomotor activity (Apryani *et al*., 2010; Chittrakarn *et al*., 2010), while a higher dose (>5mg/kg) will reduce locomotor activity (Idayu *et al*., 2011; Harun *et al*., 2015), while dose ranging from 10-30 mg/kg produce an antidepressant effect without a noticeable change in locomotor activity from lower dose (Farah Idayu *et al*., 2011). Acute administration of mitragynine (10-40mg/kg) produce anxiolytic effects (Macko *et al*., 1972; Hazim *et al*., 2014).

Studies on Kratom also show calcium channel blocking and potassium channel modulation effect, inhibiting neurotransmitter release in vas deferens, resulting in vasodilatation, anti-arhythmic, and anti-hypertensive effects (Tohda *et al*., 1997; Zhou & Zhou, 2010). Agonist activity on alpha-2 receptor also observed from Kratom. This activity is responsible for the opioid withdrawal syndrome mitigation effect of Kratom. Meanwhile, the

stimulant and anti-depressive effects are due to the 5-HT2A receptor antagonist activity of Kratom (Kumarnsit *et al*., 2007; Raini, 2017). Studies on the effects of mitragynine and kratom extract show that Kratom has a muscle relaxant effect, dose-dependent antidiarrheal effect, immunosuppressant, appetite suppressant, and upregulation of glucose transporter protein, making it a possible candidate as anti-diabetic medication (Macko *et al*., 1972; Chittrakarn *et al*., 2008, 2010; Purintrapiban *et al*., 2011).

Kratom, as discussed before, has opioid properties, thus might bear the risk of addiction. Suwanlert (1975) also reported that chronic use of Kratom can trigger withdrawal symptoms in its user. Physiological withdrawal symptoms encountered include headache, nausea, vomiting, fever, decreased appetite, tremor, muscle spasms and pain, sleeping difficulty, watery eyes/nose, hot flashes, and diarrhea. Psychological symptoms commonly reported are nervousness, sadness, restlessness, anger, tension, and depressed mood. It is to be noted that no suicidal ideation emerges, even after prolonged periods of usage (Singh *et al*., 2014). The dependence of Kratom can be treated by dihydrocodeine and lofexidine (McWhirter & Morris, 2010), and buprenorphine-naloxone (Buresh, 2018; Schmuhl *et al*., 2020). However, a study conducted by Hemby *et al*., (2019) suggests that mitragynine has no potential for abuse, and can be of use to treat opioid addiction. However, 7-HMG should be considered a high abuse potential and could increase opiates intakes.

5.2. Toxicology of kratom

The toxicology of Kratom has been studied and discussed extensively. While common side effects from kratom tea ingestion like dry mouth, constipation, nausea, sleep disorder, and diuretic (Suwanlert, 1975; Cinosi *et al*., 2015) can seem harmless, a more extensive study can give us valuable information on the toxicological properties of Kratom.

Cases reporting jaundice and intrahepatic cholestasis occurrence following a massive dose of kratom powder usage (14-21 g) for 14 days, suggesting Kratom hepatotoxicity (Kapp *et al*., 2011). This diagnosis of Kratom-induced hepatotoxicity was made based on the exclusion of all other hepatotoxicity agents. Jaundice was also reported in other cases with total bilirubin up to 33.7 mg/dL, and alkaline phosphatase up to 790 units/L. Normalization of bilirubin and alkaline phosphatase happened around 2 months after cessation, albeit the decrease can be observed in 2 to 7 days (Dorman *et al*., 2015; Tayabali *et al*., 2018; Osborne *et al*., 2019; Antony & Lee, 2019). The symptoms of liver injury are known to be resolved with N- Acethylcysteine administration, the mechanism is still unknown (Mousa *et al*., 2018). Another study also showed in vitro GST inhibiting effect of kratom that might suggest that Kratom may burden the liver to some extent, however in vivo study with rats is contradictory, albeit inconclusive (Azizi

et al., 2010). This discrepancy might occur due to CYP450 inhibition properties of mitragynine that activate alternative liver detoxification (GST) pathway, causing glutathione overconsumption that leads to its depletion. This mechanism is similar to NAPQI (N-acetyl-p-benzoquinone imine) toxicity and, to some extent, rationalizes the effect of N-Acethylcysteine on kratom induced liver injury and suggest potential interaction with certain drugs when administered concomitantly (Kong *et al*., 2011; Hanapi *et al*., 2013; Mousa *et al*., 2018).

The neurotoxicity of kratom is also discussed due to its opioid effects. Case of status epilepticus and a case of seizure followed by coma after kratom ingestion have been published (Nelsen *et al*., 2010; Oberbarnscheidt & Miller, 2019). Another case also suggests that kratom can cause posterior reversible encephalopathy syndrome (PRES) with elevated blood pressure. Supportive care and lowering blood pressure by nicardipine administration can be done to improve the patient's condition (Castillo *et al*., 2017; Alsarraf *et al*., 2019). Both acute and chronic exposure to kratom is known to be neurotoxic in both in vitro and in vivo studies using zebrafish. This neurotoxicity can be prevented or reversed by Naloxone administration (Oberbarnscheidt & Miller, 2019; Ramli *et al*., 2019). This indicates that kratom may have pro-convulsant activity although the mechanism is still unknown, some suggested that the mechanism may be similar to that of tramadol (Nelsen *et al*., 2010; Alsarraf *et al*., 2019).

The first scientific evidence of kratom cardiotoxicity is published by Lu *et al*., (2014). The studies found that mitragynine and its analogs can exhibit significant IKr suppression in hERG-HEK cells in low concentration (IC50 0.91-2.47 µM) and induce arrhythmia. Case reports of supposedly kratom cardiotoxicity have been reported following cases of cardiorespiratory arrest following ingestion of kratom. Aggarwal *et al*., (2018) postulate that some of the compounds in kratom are had cardiotoxic or calcium channel blocking properties. Two cases of Acute Respiratory Distress Syndrome (ARDS) following kratom and alcohol ingestion have been reported. Both cases developed into hypoxemic respiratory failure (Chittrakarn *et al*., 2010; Pathak *et al*., 2014).

Ingestion of kratom during pregnancy is known to induce neonatal abstinence syndrome (NAS) that manifests after 24 hours - 2 days postpartum, exhibited the classic symptoms of opioid withdrawal such as sneezing, jitteriness, excessive suck, and facial excoriation. The newborn patients are then transferred into NICU and treated with Morphine (Mackay & Abrahams, 2018; Davidson *et al*., 2019) or, in case of inadequacy, Clonidine (Eldridge *et al*., 2018).

6. Analytical Method

Attempts at Kratom analysis and its metabolite substances have been done. A few of the analysis method developed is shown in Table 1. Liquid chromatography (HPLC and UPLC) coupled with mass spectrometer detector seem to be the preferred method for identifying and analyzing kratom. This most likely happened due to HPLC as a mature technology and accessibility, and also mass spectrometer sensitivity. Other novel methods are also studied, namely DART-MS and ELISA. DART-MS method to directly analyze plant material is developed by (Lesiak *et al*., 2014), in which part of plant material is analyzed directly by suspending it between the ion source and mass spectrometer inlet. Lee *et al*., (2020) developed mitragynine detection using ELISA with a polyclonal antibody. Based on the previous iteration using a monoclonal antibody, polyclonal antibody offers the ability to detect multiple epitopes, thus providing more robust and greater sensitivity for detection. Unfortunately, kratom identification is not a standard practice in most hospitals, resulting in a scarcity of kratom toxicity data.

7. Legal Status

Due to the opioid activity and increased use of Kratom, the plant is deemed illegal in some countries. In 1979, the Thai government placed Kratom under Schedule 5 of the Thai Narcotics Act, thus deemed it illegal to buy, sell, import, or possess it. The law also makes planting trees illegal and requires cutting down existing ones. However, in January 2021, the Thailand parliament voted to pass an amendment bill to remove kratom from the narcotics list. In Malaysia, the use was permitted until 2003, when it was placed under The Poison Act making selling and possession of M. speciosa leaves or its preparations an offense. As of September 2019, the Malaysian government is considering amending the act so that planting Kratom requires permission (Vicknasingam *et al*., 2010; Yusof, 2019; Sattaburuth & Wannapiroon, 2021). In Indonesia, Kratom is legally cultivated and exported on large scale to Asia, North America, and Europe. However, in 2008 it was banned for use in processed food and later in 2016 restricted for sale as traditional medicine and expected to be deemed illegal in 2022 by Indonesia FDA (Tanguay, 2011; Hassan *et al*., 2013; Badan Pengawas Obat dan Makanan, 2016; Rokib, 2019; Andilala, 2019). However, in February 2020 Indonesia's Ministry of Agriculture enlisted Kratom under medicinal plants classification, making its legal status in limbo (Menteri Pertanian Republik Indonesia, 2020).

Kratom or its component legal status is varied greatly between countries. The drug is controlled in Denmark, Latvia, Poland, and Sweden. It is prohibited to sell in the UK under the Psychoactive Substance Act 2016. Meanwhile in the US and Germany kratom or its substance

are currently not controlled substances but under surveillance (Chittrakarn *et al*., 2012; EMCDDA, 2012; Great Britain, 2016; Departement of Health, 2017; Raini, 2017; Food and Drug Administration, 2018). The FDA has issued a statement that M. speciosa products remain unapproved either as a dietary supplement or drug and deemed illegal for interstate commerce. The FDA also encourages importers and all companies involved in M. sp The species first described by the Dutch botanist, Pieter Willem Korthals, later transferred the species to another genus, Stephegyne. Other authors also transferred and renamed the species *Nauclea korthalsii* (Steudel 1841), *Nauclea luzoniensis* (Blanco 1845), *Nauclea speciosa* (Miquel 1856). In his revision of the tribe Naucleeae, Haviland (1897) transferred the species back into the genus Mitragyna and set the currently accepted species name as *Mitragyna speciosa* (Korth.) Havil. eciosa product commerce to remove their products from the market. Meanwhile, the Drug Enforcement Administration (DEA) has placed Kratom on the Drugs and Chemicals of Concern list, which suggests that the agency may eventually try to ban it in the US once sufficient evidence is acquired (Veltri & Grundmann, 2019).

8. Discussion and Conclusion

Kratom has always been used as a remedy in various parts of southeast Asia, and with the advancement of technology, it can be procured quite easily around the globe (Ratsch, 2005; Cinosi *et al*., 2015). Its unique phytochemical composition and potential as both treatments for addiction and substance of abuse made kratom legal status, not a black-and-white situation. With the interest in kratom growing, and easier for the public to purchase, more study about kratom is conducted for a better understanding of the benefits and risks that can be obtained from it.

Addiction is one of the main concerns of Kratom use in society, which can lead to many undesired adverse effects to occurs. While mitragynine, the main alkaloids of Kratom, have no potential for abuse (Hemby *et al*., 2019) a small portion of 7-HMG could overturn that as it has 13-fold higher potency than morphine, and 46-fold higher potency than mitragynine (Matsumoto *et al*., 2004). This means that removing or preventing 7-HMG formation could be key to overcoming the abuse potential of Kratom consumption. Changes in the growth environment can be used to engineer the alkaloid formation to desired results, where mitraphylline appears to become the major alkaloid compound in Kratom grown on USA soil (León *et al*., 2009).

Table 1. Kratom analytical method developed for various sample matrixes

Sample	Method	Author
Plant Extract and Product	GC-FID: HP-5 capillary column (30 m × 0.25 mm id, 0.25 µm). Starting temperature 200oC for 2 minutes, 10oC/min up to 300oC, hold for 20 minutes. Injector and detector temperature 280oC. GC-MS: DB-5 capillary column (30 m × 0.25 mm id, 0.1 µm). Starting temperature 200oC for 2 minutes, 10oC/min up to 300oC, hold for 20 minutes. Injector and detector temperature 280 oC.	(Chan et al., 2005)
Plant Extract	LC-ESI-MS: LC: C18 (2 x 150 mm x 5 µm) at 40°C. Mobile phase: gradient of 10 mM ammonium formate, pH 3.5/methanol at 0.3 ml/min. Wavelength: 190-400 nm. MS: Nitrogen gas 13 l/min at 330°C; nebulizer gauge pressure, 345 kPa; vaporizer temperature, 350°C; capillary voltage, 3500 V; fragmentation voltage, 100 V. Spectra mass range 100–600 m/z.	(Kikura-Hanajiri et al., 2009)
Plant Extract	TLC: Silica gel plates 60 F254 with hexane/ethylacetate/25% ammonia solution (30:15:1 v/v/v) as mobile phase. HPLC: Luna C18(2) 250 x 4.6 mm, 5 µm. Mobile phase: Acetonitrile/0.01% ammonia solution (7:3 v/v), pH 10.3, flow rate 1ml/min.	(Kowalczuk et al., 2013)
Plant Extract	GC/MS: DB-5 capillary column (30 m × 0.25 mm id, 0.25 µm). Starting temperature 200 oC for 2 minutes, 10 oC /min up to 325 oC, hold for 20 minutes. Inlet temperature 25 oC. Full scan spectra at 397 m/z. UPLC/PDA: C18 (100 x 2.1 mm, 1.7 µm). Mobile phase: gradient of 0.1% aqueous formic acid/acetonitrile for 0.5 mL/min. PDA wavelength: 254 nm. LC-MS/MS: C18 (100 x 2.1 mm x 3.5 µm). Mobile phase: gradient of 0.1% aqueous formic acid/acetonitrile for 0.3 mL/min. PDA wavelength: 254 nm. sheath gas (N2, 50 arbitrary units); auxiliary gas (N2, 5 arbitrary units); capillary temperature, 300 oC; spray voltage 3.5kV.	(Casey et al., 2015)
Plant extract	DART-MS: Parameters: 350 oC gas heater temperature; ring lens voltage, 5 V; orifice 1 voltage, 20 V; orifice 2 voltage, 5 V; and ion guide voltage 600 V. Spectra mass detection above 60 m/z	(Fowble & Musah, 2019)
Plant material	DART-MS: Parameters: 250 V grid voltage; 350 oC gas heater temperature; ring lens voltage, 5 V; orifice 1 voltage, 20 V; orifice 2 voltage, 5 V; and peak voltage 600 V. Spectra mass range: 50–800 m/z at 1 spectrum per second.	(Lesiak et al., 2014)
Isolate	UHPLC-MS-DAD: C8 (2.1 x 100 mm, 1.8 µm). Temperature: 30oC. Mobile phase: gradient of Acetonitrile/water (ammonium acetate pH 7.7), 0.3 ml/min. DAD wavelength: 220 and 254 nm. Spectra mass range: 100–800 Da. SFC-DAD: Agilent Rx-Sil column (2.1x50 mm, 1.8 µm). 180 bar back pressure, 0.5 mL/min flow rate at 25 oC. Eluent: gradient of CO2/10 mM ammonium acetate in Methanol. GC-MS: Column: 5% phenyl methyl polysiloxane (30 m x 0.25 mm x 0.25 µm) 1 mL/min flow rate,	(Wang et al., 2014)

Sample	Method	Author
	25:1 split ratio. Starting temperature 220 oC at 8 oC /min up to 300 oC. Spectra mass range: 35–550 Da.	
Product	HPLC: C8 (150 x 4.6 mm x 5 µm) at 35 oC. Mobile phase: is oC ratic methanol/water (80:20) at 0.5 mL/min. Wavelength: 221 and 291 nm.	(Chittrakarn et al., 2012)
Human urine	HPLC-MS/MS: Silica (50 x 3 mm x 3 µm) at 40 oC. Mobile phase: gradient of 5 mM ammonium acetate/methanol at 0.25 mL/min.	(Lu et al., 2009)
Human urine	LC-MS/MS: C18 (100 mm x 2.1 mm x 5 µm) at 28 oC. Mobile phase: gradient of water/acetonitirile/0.1% (v/v) formic acid in methanol at 0.2 mL/min. Sheath gas (nitrogen) pressure: 30 a.u.; auxillary gas (nitrogen) pressure: 20 a.u.; collision gas (argon) pressure: 1.5 mTorr; capillary temperature: 350 oC; spray voltage: 5000 V; ion source: positive ESI mode. MS acquisition time: 2.5 min; scan width: 0.01 m/z; scan time: 0.06 s; peak width Q1 and Q3: 0.7 FWHM	(Arndt et al., 2011)
Human urine	UPLC-MS/MS: T3 (2.1 x 50 mm x 1.8 µm) at 50 oC. Mobile phase: gradient of 0.1% formic acid in 10mM ammonium acetate/acetonitrile at 0.5 mL/min. Spectra mass range: 90–600 Da. LC-MS/MS: C18 (2.1 x 100 mm x 5 µm) at 50 oC. Mobile phase: gradient of 0.1% formic acid in 10mM ammonium acetate/acetonitrile at 0.5 mL/min. curtain gas, 38 psi; ion spray, 3800 V; temperature, 5008C; gas 1 and 2, both 63; declustering potential, 60 V; entrance potential, 10 V; exit potential, 19 V.	(Le et al., 2012)
Human urine	LC-MS/MS: phenyl-hexyl (100 mm x 2.1 mm x 2.6 µm) at 40 oC. Mobile phase: gradient of 0.1% formic acid in water/acetonitrile at 0.4 mL/min. Ion spray voltage 2500 V, temperature 600 oC.	(Fu et al., 2015)
Human urine	HPLC-DAD: C18 (150 mm x 2.1 mm x 5 µm). Mobile phase: gradient of methanol/0.1% H3PO4 at 0.5 mL/min. Wavelength: 222 nm.	(Neng et al., 2015)
Human urine	ELISA: HRP-MG and immunogen MG-cBSA were incubated for 1 h and washed. Color reaction: 150 µL TMB (3,3',5,5'-tetramethylbenzidine) added and incubated for 30 min. 50 µL 2N HCl was added to stop the reaction. Wavelength: 450 nm.	(Lee et al., 2020)
Human hair	LC-MS/MS: C18 (50 x 2.1 mm x 2.6 µm). Mobile phase: gradient of 10mM ammonium formate buffer pH 3.4/methanol at 0.5 mL/min. Probe temperature (TEM) of 550 oC, curtain gas (CUR) of 30 psi, a nebulizer gas (GS1) of 45 psi, a nebulizer current (NC) of 3 V, and an ion spray voltage (IS) of 5500 V. The entrance potential (EP) and collision cell exit potential (CXP) was set to 10 V and 42 V.	(Meier et al., 2020)
Plasma	HPLC: C8 (150 mm x 4.6mm x 5µm). Mobile phase: Acetonitrile/50 mM ammonium acetate pH 5 (50:50) at 1mL/min. Wavelength: 223 nm.	(Parthasarathy et al., 2010)

Method to exempt 7-HMG from kratom or its product could prove to be beneficial as the risk of addiction can be minimized, thus preventing overconsumption and upscaling dose that common on kratom addiction that could lead to various toxicity such as hepatotoxicity (Dorman *et al*., 2015), neurotoxicity (Ramli *et al*., 2019), neonatal abstinence syndrome (Eldridge *et al*., 2018) and even death. With the increasing popularity and easier procurement of kratom, the increasing number of deaths attributed to kratom year by year (Corkery *et al*., 2019) seems inevitable. Thus, a better understanding of the toxicity mechanism and treatment of kratom became more valuable in short term. Even though morphine (Eldridge *et al*., 2018), naloxone (Ramli *et al*., 2019), and acetylcysteine (Mousa *et al*., 2018) can be used as a treatment for kratom toxicity, it is symptomatic by nature and can lead to unknown risk due to poor understanding. Thus, further research is needed.

Case report of kratom toxicity is scarce as physicians are not yet aware of Kratom risk, and analysis of Kratom compounds in biological samples from inpatients is not yet a standard practice in many hospitals. That makes the diagnosis of kratom toxicity or death rely on the history of the patients. This leads to many cases related to kratom toxicity or deaths might be overlooked. Analysis with HPLC system is easy to adapt, and with readily available solvents like methanol, acetonitrile, and water, adapting these methods should prove beneficial.

In summary, Kratom's legal status and confusion are related to 7-HMG as the most potent opioid compounds present that bear risk of abuse. While Kratom can be cultivated and developed as opioid addiction treatment, the presence of 7-HMG, if not controlled properly, might undermine its potential. Thus reducing 7-HMG might prove to be beneficial for reducing the risk of toxicity from Kratom overdoses, such as hepatotoxicity, neurotoxicity, neonatal abstinence syndrome, and many more. It should be pointed out that a small dose of kratom provides very little risk, even though a larger dose might lead to addiction and prove to be fatal. Various methods have been developed to detect Kratom in various matrixes, including beverages and biological samples. Even though nowadays it’s not yet a common practice in hospitals, adapting such methods could prove to be beneficial to provide a better understanding of how Kratom works in the human body.

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Conflict of Interest

All authors declared that there was no conflict of interest

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