



Pre-Review Report:

Kratom (*Mitragyna speciosa*), mitragynine, and
7-hydroxymitragynine

Expert Committee on Drug Dependence
Forty-fourth Meeting
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Executive Summary

Kratom is the common term for *Mitragyna speciosa*, a tree native to Southeast Asia. The kratom leaf contains more than 50 alkaloids. The two main known psychoactive compounds in kratom leaf are the indole alkaloids mitragynine, comprising up to two-thirds of the alkaloid content, and 7-hydroxymitragynine, which comprises about 1% of alkaloid content and is also formed by metabolism of mitragynine *in vivo*. Several total synthesis of mitragynine have been developed, but require too many steps and provide the final product in very low yields. Hence, extraction of the compound seems to be more convenient. 7-Hydroxymitragynine can also be obtained from mitragynine by a single step chemical reaction. *M. speciosa* can be identified macroscopically by examining the leaf, although this analysis can be misleading as the leaves from plants of the same tribe or genus are very similar. Numerous analytical methods have been reported in the literature for the identification and quantification of kratom alkaloids, particularly mitragynine, in a wide range of samples, including commercial samples, raw plant material and biological specimens. The most applied methods include chromatographic techniques coupled to either spectrophotometric or mass spectrometric detectors.

Indigenous populations have used kratom products for centuries as herbal medicine to treat various medical conditions (especially pain and opioid withdrawal), to enhance sociability, and to increase energy and reduce fatigue (especially among manual workers). Lower doses reportedly have stimulant-like effects, while higher doses have opioid-like effects. Kratom use is almost exclusively oral, typically by chewing the leaves, ingesting powdered leaf, or drinking a kratom tea or decoction (Southeast Asia) or by ingesting powdered leaf as a capsule or pill or dissolved in a beverage (US, Western Europe). Processed kratom products sold commercially often contain other compounds.

Kratom is not currently controlled under the UN conventions. Some countries ban kratom or limit its use for human consumption. The Association of Southeast Asian Nations (ASEAN) bans kratom in herbal medicine or dietary supplements, but allows cultivation of the tree. Kratom is legal in the United States at the federal level, but is considered a drug of concern by the US Drug Enforcement Administration.

Kratom is almost always taken orally. In Southeast Asia, typical formulations include raw or powdered leaves or liquid leaf-extracts (tea or decoction). Kratom decoction is often mixed with another beverage to create a kratom “cocktail.” In the United States and Western Europe, common formulations include leaf powders taken as a tablet or capsule or dissolved in a beverage. Mitragynine and 7-hydroxymitragynine have been found in resins and liquids sold online for use in electronic drug delivery devices (so-called “e-cigarettes”).

In the absence of accurate labeling of kratom products, it is impossible to know the actual doses of kratom alkaloids ingested by kratom users. Surveys of convenience samples of kratom users in Southeast Asia suggest that a typical daily dose of liquid formulations is

3-6 glasses/day, containing an estimated 200-400 mg of mitragynine. Surveys of convenience samples of US kratom users suggest that a typical daily dose of powder formulations is 2-6 g/day, although heavy users may ingest up to 20 g/day.

The pharmacokinetic parameters of oral mitragynine in rats, when given as the isolated alkaloid, are T_{max} of 1.3-4.5 hours, C_{max} of 400-700 ng/mL, half-life of 3.3-9.4 hours, and oral bioavailability of 3%-17%; when given as lyophilized kratom tea or organic extract of kratom tea, T_{max} of 0.3 or 1.0 hours, respectively, C_{max} of 0.55 and 0.66 ng/mL, respectively, and oral bioavailability of 25.1% and 31.2%, respectively. The pharmacokinetic parameters of isolated oral mitragynine in beagle dogs are T_{max} of 0.3 hours, C_{max} of 278 (± 47) ng/mL, half-life of 8.7 (± 0.2) hours, and bioavailability of 69.6%.

We are aware of two published studies of humans administered controlled doses of kratom products (decoction, tea), involving 36 young adult men in Southeast Asia who used kratom daily. Pharmacokinetic parameters were T_{max} 0.84 (± 0.35) hours and 2.0 (± 0.8) hours, C_{max} 50-100 ng/mL and 1884 (± 1056) ng/mL, and half-life 23 (± 16) hours. There are currently no human data on the oral bioavailability of mitragynine or 7-OH-mitragynine, either alone or as part of a kratom product. Given this lack of knowledge, and the known variability in oral bioavailability between rodents and beagle dogs, it is impossible to accurately extrapolate to humans from the animal dosing of kratom and kratom alkaloids. We are not aware of any *in vivo* human studies on the metabolism of kratom alkaloids or kratom-drug interactions. Mitragynine inhibits activity of some human liver cytochrome P450 enzymes in liver cells *in vitro* and enhances the activity of others. These findings raise the potential for clinically significant kratom-drug interaction in human kratom users.

Mitragynine and 7-hydroxymitragynine act as partial agonists at the mu-opioid receptor (mOR). 7-Hydroxymitragynine has 5-23 times more binding affinity and 5-20 times more intrinsic activity (receptor activation) than does mitragynine. For comparison, morphine has 8-10 times more binding affinity and 3 times more intrinsic activity than does 7-OH-mitragynine. Activation of the mu-opioid receptor is considered responsible for most of the pharmacological effects of kratom alkaloids. Kratom alkaloids are biased mOR agonists in that they activate the G-protein coupled intracellular pathway but not the beta-arrestin pathway. This may confer some selectivity in producing analgesia with less respiratory depression or physical dependence. Kratom alkaloids also act as competitive antagonists at the kappa- and delta-opioid receptors, but with lesser potency. Mitragynine binds to alpha1- and alpha2-adrenergic receptors, serotonin-1A and -2A receptors, and the dopamine D1 receptor. The functional significance of such binding is unknown.

Extracts of the kratom leaf, mitragynine, and 7-hydroxymitragynine have a variety of behavioral effects in rodents after oral or intraperitoneal administration. Extrapolating these findings to humans is uncertain because of potential species differences in pharmacokinetics, especially oral bioavailability. Most studies focus on the opioid-like effects, including analgesia, slowed gastrointestinal transit, development of naloxone-precipitated opioid-like withdrawal symptoms (but not spontaneous withdrawal symptoms) after repeated daily (at least 4-5 days) dosing, and suppression of naloxone-precipitated

opioid withdrawal. Repeated daily dosing (at least 4-5 days) produces tolerance to the opioid-like effects and cross-tolerance with opioids.

Kratom and kratom alkaloids have inconsistent effects in rodent models of reward. Like morphine, kratom and mitragynine have rewarding effects in conditioned place preference. Unlike morphine, they do not support drug self-administration. Mitragynine has no effect on intracranial self-stimulation (ICSS), while 7-OH-mitragynine had no effect in one study and lowered ICSS threshold (rewarding) in another study. Rats distinguish mitragynine from saline, but not from morphine. One study found that kratom methanolic extract did not increase dopamine concentration in the mouse brain nucleus accumbens. Such increases are produced by almost all substances abused by humans, including opioids.

Kratom and mitragynine have little or no effect on motor activity and sleep in rodents, but reduce opioid and alcohol self-administration and withdrawal and improve behavior in rodent models of anti-depressant and anti-psychotic action.

Acute and chronic (up to 6 weeks) studies in rodents, dogs, and cats show little toxicity from mitragynine or 7-hydroxymitragynine at oral or i.p. doses below 50 mg/kg, except for reduced food and water intake and weight loss. Higher doses produce respiratory suppression, liver damage, and seizures. The mitragynine oral LD50 is around 500 mg/kg in mice and >800 mg/kg in rats. For comparison, the oral LD50 of mitragynine is 600 mg/kg in mice and 461 mg/kg in rats. The oral bioavailability of mitragynine in humans is unknown, so extrapolation from rodent to human doses is uncertain.

Recent large, nationally representative epidemiological surveys in Thailand (2017) and the US (2019) suggest that 2-3% and 0.7%, respectively, of the adolescent/adult population are past-year users of kratom. There are little other good-quality data on the epidemiology of kratom use and kratom use disorder. Most data come from online surveys of self-selected convenience samples of adult kratom users. One such 2017 survey in the US found that 12.3% of respondents met DSM-5 criteria for past-year kratom use disorder. Cross-sectional surveys in Southeast Asia and the US find that up to one-half to three-quarters of chronic daily kratom users report difficulty in stopping their kratom use and experience opioid-like withdrawal symptoms when they do stop, occurring within 48 hours of stopping. However, few such kratom users report psychosocial or medical problems from their use. Case reports of kratom users seeking medical attention for kratom withdrawal find use patterns of up to 15-20 g daily of kratom products.

There are only three small published clinical studies on the human pharmacology of oral kratom products (tea, decoction, or extract) involving a total of 41 young adult men. One study of 26 chronic kratom users in Malaysia found that mitragynine (1.6 mg/kg in the form of kratom decoction) doubled pain tolerance in the cold pressor test about one hour after ingestion. A third study of five kratom-naïve British adults found that kratom extract reduced pain-sensitivity. All three studies reported only transient, clinically insignificant adverse effects.

Kratom can produce serious toxicity in high-dose users, but the number of cases is probably low as a proportion of the total number of users. More than 300 deaths associated with kratom have been reported since 2010, the vast majority since 2015 and almost all in the US and Western Europe. Attributing causality to kratom can be difficult, as most cases involve multiple substances and few cases involved comprehensive toxicology to detect other substances. In one large case series, 23% of deaths had no other substances identified or considered contributory. In some smaller case series that had intensive forensic investigation, no kratom-associated deaths are found to be caused by kratom. In addition, there is no association between mitragynine concentrations in post-mortem blood and likelihood of a death being considered caused by kratom. At least 92 cases of kratom-associated liver toxicity have been reported. These usually resolve after cessation of kratom use; only one case required liver transplantation. Among the 3,484 kratom-associated cases reported to the US National Poison Data System from 2014-2019, in 63% kratom was the only identified substance. Among these, only 0.8% were considered medically serious (including death). The major toxicities were neuropsychiatric (agitation, confusion, sedation, hallucinations, tremor, seizure, coma) 75.4%, cardiovascular (tachycardia hypertension) 44.5%, gastrointestinal (abdominal pain, nausea, vomiting) 25.2%, and respiratory (respiratory depression) 12.1%. Small cross-sectional studies of chronic kratom users in Southeast Asia find no evidence of clinically significant cardiac, renal, or hematological abnormalities. A study comparing kratom-associated poison control center reports in the US and Thailand from 2010-2017 found similar types of adverse events in both countries. Medical severity was significantly greater in the US, although Thailand had a greater prevalence of cases with other substances mentioned.

Surveys of convenience samples of kratom users in Southeast Asia and the US find that the vast majority report using kratom to self-medicate pain, opioid withdrawal or opioid use disorder, anxiety, or depression, rather than for recreational purposes. This anecdotal evidence, plus some of the potentially beneficial behavioral effects seen in rodent studies, have generated proposals to develop kratom or its alkaloids as medication for such disorders.

1. Substance identification

A. *International Nonproprietary Name (INN)*

KRATOM

No information could be identified.

MITRAGYNINE

No information could be identified.

7-HYDROXYMITRAGYNINE

No information could be identified.

B. *Chemical Abstract Service (CAS) Registry Number*

KRATOM

Not applicable.

MITRAGYNINE

4098-40-2 (-)-Mitragynine free base

1908497-94-8 (+)-Mitragynine free base

36455-45-5 Mitragynine hydrochloride

58375-35-2 Mitragynine hydriodide

11047-38-4 Mitragynine hydrobromide

11047-42-0 Mitragynine perchlorate

11047-41-9 Mitragynine oxalate

11047-35-1 Mitragynine cinnamate

11047-36-2 Mitragynine trichloroacetate

36455-46-6 Mitragynine ethanedisulfonate

11047-37-3 Mitragynine, compd. with 1,3,5-trinitrobenzene (1:1)

7-HYDROXYMITRAGYNINE

174418-82-7 7-Hydroxymitragynine

C. *Other Chemical Names*

KRATOM

Not applicable

MITRAGYNINE

Corynan-16-carboxylic acid, 16,17-didehydro-9,17-dimethoxy-, methyl ester, (16E,20β)- (ZCI)

Corynantheidine, 9-methoxy- (7CI)

Mitragynine (6CI)

(-)-Mitragynine

9-Methoxycorynantheidine

Indolo[2,3-a]quinolizine-2-acetic acid, 3-ethyl-1,2,3,4,6,7,12,12b-octahydro-8-methoxy- α -(methoxymethylene)-, methyl ester, [2S-[2 α (E),3 α ,12b β]]-

Mitragynin

7-HYDROXYMITRAGYNINE

Corynan-16-carboxylic acid, 1,2,16,17-tetradehydro-2,7-dihydro-7-hydroxy-9,17-dimethoxy-, methyl ester, (7 α ,16E,20 β)- (ZCI)

7-Hydroxymitragynine

7 α -Hydroxy-7H-mitragynine

9-Methoxycorynantheidine hydroxyindolenine

Mitragynine hydroxyindolenine

D. Trade Names

KRATOM

M. speciosa is available online and in shops that sell equipment for smoking cannabis and tobacco ('head shops') and the derived products are often distinguished according to vein color, "provenance" (origin) and potency. Three kinds of kratom with varying leaves and potency have been described, for example, red veined (called "Kan daeng" in Thai), white veined (known as "Tang gua") and a third kind 'Yak yai', which have two small teeth-like formations near the apex of the leaf (Suwanlert, 1975)(Sukrong et al., 2007).

Several further types of kratom are present online with the following names (Raffa, 2014):

Premium kratom

Commercial grade kratom

Bali kratom

Enhanced Bali kratom

Ultra enhanced Indo (U.E.I.) kratom

Indo red vein, Malaysian kratom

Red vein Thai kratom

Green- or white-vein Thai kratom

Maeng Da kratom

White-veined Borneo kratom

New Guinea kratom

Java kratom

Sumatra red

The Rifat strain

The bumblebee strain

Red Riau

Green Riau.

According to other studies, the “strain” of kratom reporting the vein color actually corresponds to the leaf age (Braley and Hondrogiannis, 2020). For example, the red vein “strain” is younger and more potent compared to the mature green vein “strain”, grows more abundantly in Southeast Asia and is slightly more persistent than other *M. speciosa* trees. The red-vein “strain” is marketed with several names including (Kratomgardens):

Borneo Red

Red Vein Sumatra

Pontianak Red Horn

Red Thai.

White vein kratom is known as (Kratomgardens):

White Vein Sumatra

Borneo White

Pontianak White Horn.

The green vein is described as a mix of the red and the white type and is called Malaysian Green or Pontianak Green Horn (Kratomgardens).

Todd et al. investigated the chemical composition of over 50 commercial kratom products, all with different names, belonging to the red, white and green vein "strains" (Todd et al., 2020).

E. Street Names

Kratom is the common term used for the *Mitragyna speciosa* leaf and products derived from the leaf. Street names in Southeast Asia include krathom, kakuam, ithang or thom (Thailand), biak-biak or ketum (Malaysia), and mambog (Philippines). Kratom “cocktail” refers to a decoction of kratom leaves mixed with another beverage. In Germany, krypton refers to a mixture of kratom and O-demethyltramadol (Phillipp et al., 2011).

F. Physical Appearance

KRATOM

Marketed kratom products usually consist of light to dark green crushed or powdered dried leaves (EMCDDA, 2015). Moreover, vendors offer powdered, greenish or beige-brown preparations fortified with extracts from other leaves. Also, aqueous decoction of kratom leaves can be used to make paste-like extracts and dark brown kratom resin by partially or fully boiling down the water. Lastly, tinctures and capsules filled with powdered kratom are also supplied (EMCDDA, 2015).

Botanic description:

Kratom, commonly referred to *Mitragyna speciosa* (Korth.) Havil., is a tropical tree that grows in Thailand, Myanmar, Malaysia, Borneo, Sumatra, the Philippines, and New Guinea (Raffa, 2014). *Mitragyna* Korth. is a small genus of the Rubiaceae family. The genus *Mitragyna* belongs to the tribe Naucleae of the subfamily Cinchonoideae (Razafimandimbison and Bremer, 2001).

The genus *Mitragyna* contains ten species, of which four species occur in Africa (*M. inermis*, *M. ledermannii*, *M. rubrostipulata*, and *M. stipulosa*), and six species in South and Southeast Asia, spread between India and New Guinea (*M. speciosa*, *M. tubulosa*, *M. rotundifolia*, *M. parvifolia*, *M. hirsuta*, and *M. diversifolia*).

The nomenclatures of *M. speciosa* have been changed by various authors over the years. First described by the Dutch botanist Pieter Willem Korthals (1807–1892) (Korthals, 1839), the genus was renamed and reclassified several times until George Darby Haviland gave the final name and classification in 1897 (Haviland, 1897).

M. speciosa is an evergreen tree that reaches 25-meter height and 0.6- to 0.9- meter diameter. It generally presents a straight trunk, a smooth and gray outer bark and a pinkish inner bark (Raffa, 2014). The petiolate leaves are generally dark glossy and green in color and elliptical in shape., and; they can reach 14-20 cm in length and 7-12 cm in width. They typically present 12-17 pairs of veins. The flowers are arranged in groups of three heads, one with a short peduncle head between two heads with longer peduncle. The heads have a diameter of 1.5-2.5 cm with a light hairy interfloral 4-6 mm long bracts. The flower calyx is about 2 mm long with 5 lobes. The corolla appears as funnel-shaped with an intense yellow color. The corolla tube measures 3.5-5 mm, while the corolla lobes are 2.5-3 mm long and hairless with a revolute margin and a distinct ring of hairs within the base of the lobes.

The fruiting heads are 2-3 cm wide, with 10 ribbed fruits of 7-9 mm length and 4-5 mm width. They contain numerous flat seeds, which are about 1 mm long with a 1-2 mm paper wing at each end (Raffa, 2014, Haviland, 1897, Ridley, 1923).

Synonyms for *Mitragyna speciosa* Korth. (Havil.) (Raffa, 2014):

Nauclea korthalsii Steud.; *Nauclea luzoniensis* Blanco; *Nauclea speciosa* (Korth.) Miq.; *Stephegyne speciosa* Korth.

Common names used for *Mitragyna speciosa* Korth. (Havil.) (Raffa, 2014):

Indonesia: kadamba (Kelantan), puri (Batak Toba, Sumatra), keton

Malaysia: biak, biak-biak, ketum, kutum, pokok biak, pokok ketum, sepat (Sabah)

Myanmar: beinsa, bein-sa-ywat

Philippines: mambog (Tagalog), lugub (Mandaya), polapupot (Ibanag)

Thailand: ithang (central), thom (peninsular), bai krathom, gratom, kakaum, katawn, krathawm, kratom, kraton

Vietnam: giam d[ef]p, giam l[as] nh[or].

Marketed kratom products:

A mix of kratom extract combined with codeine or diphenhydramine containing cough syrup, soda, ice, and potentially other pharmaceuticals, drugs, or chemicals, is referred to as “4x100” (Tungtananuwat and Lawanprasert, 2018, Ahmad and Aziz, 2012, DEA, 2019). Kratom is often sold for recreational use as either whole or crushed leaves, leaf powder, encapsulated powder, concentrated extracts (5x to 100x), solid resin or tinctures. Kratom extracts or raw material are also used as dietary ingredients as part of dietary supplements (Hilmas and Fabricant, 2014). Lastly, live plants and seeds are also available online (Raffa, 2014).

MITRAGYNINE

White, amorphous crystals (EMCDDA, 2015)

7-HYDROXYMITRAGYNINE

Amorphous powder (Horie et al., 2005).

G. WHO Review History

Kratom has not been formally reviewed by WHO and is not currently under international control. Kratom has been under ECDD surveillance due to country level reports of the abuse liability of its main psychoactive ingredient, mitragynine, and from international organization reports regarding reported fatalities. A pre-review was initiated following a proposal from an international organization with supporting information regarding fatalities due to kratom use.

2. Chemistry

A. Chemical Name

IUPAC Name:

KRATOM

Not applicable

MITRAGYNINE

Methyl (E)-2-[(2S,3S,12bS)-3-ethyl-8-methoxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl]-3-methoxyprop-2-enoate

7-HYDROXYMITRAGYNINE

Methyl (2E)-2-[(2S,3S,7aS,12bS)-3-ethyl-7a-hydroxy-8-methoxy-1,2,3,4,6,7,7a,12b-octahydroindolo[2,3-a]quinolizin-2-yl]-3-methoxyprop-2-enoate

CA Index Name:

KRATOM

Not applicable

MITRAGYNINE

Indolo[2,3-a]quinolizine-2-acetic acid, 3-ethyl-1,2,3,4,6,7,12,12b-octahydro-8-methoxy- α -(methoxymethylene)-, methyl ester, (α E,2S,3S,12bS)- (9CI, ACI)

7-HYDROXYMITRAGYNINE

Indolo[2,3-a]quinolizine-2-acetic acid, 3-ethyl-1,2,3,4,6,7,7a,12b-octahydro-7a-hydroxy-8-methoxy- α -(methoxymethylene)-, methyl ester, (α E,2S,3S,7aS,12bS)- (9CI, ACI)

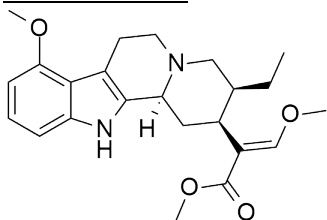
B. Chemical Structure

Free base:

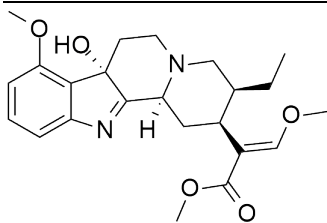
KRATOM

Not applicable

MITRAGYNINE



7-HYDROXYMITRAGYNINE



Molecular Formula:

KRATOM: Not Applicable

MITRAGYNINE: C₂₃H₃₀N₂O₄

7-HYDROXYMITRAGYNINE: C₂₃H₃₀N₂O₅

Molecular Weight:

KRATOM: Not Applicable

MITRAGYNINE: 398.50 g/mol

7-HYDROXYMITRAGYNINE: 414.50 g/mol

C. Stereoisomers

KRATOM

Not Applicable

MITRAGYNINE

The presence of three stereogenic centers and an *E-Z* isomerism in the double bond on the methoxy acrylate group lead to the possibility of 16 different stereoisomers. However, only four stereoisomers occur naturally in *M. speciosa*: mitragynine, which has the 3*S*,15*S*,20*S* configuration (1); speciociliatine 3*R*,15*S*,20*S* (2), speciogynine 3*S*,15*S*,20*R* (3), and mitraciliatine 3*R*,15*S*,20*R* (4) (Figure 1). The *E*- stereochemistry is always present in the double bond on the C-15 methoxy acrylate group in mitragynine stereoisomers isolated from *M. speciosa* (Ramanathan et al., 2021). Of these four stereoisomers, mitragynine (1) is the most abundant, reaching up to 66% of the total alkaloid content in kratom leaves, while speciociliatine (2) and speciogynine (3), combined together, account for an average of 8-9%. Mitraciliatine (4) is the least abundant, with less than 1% of the total alkaloid content (Ramanathan et al., 2021)(Figure 1).

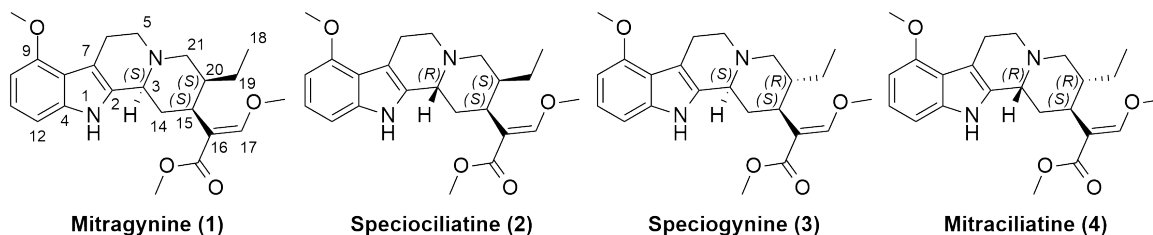


Figure 1. Naturally occurring stereoisomers of mitragynine. Atom numbering is shown in the main component (1). Absolute configurations are indicated.

7-HYDROXYMITRAGYNE

The presence of four stereogenic centers and an *E-Z* isomerism in the double bond on the methoxy acrylate group generate 32 potential stereoisomers, but only three are found in *M. speciosa*: 7-hydroxymitragynine, which has the 3*S*,7*S*,15*S*,20*S* configuration (5), 7-hydroxyspeciociliatine 3*R*,7*R*,15*S*,20*S* (6), and 7-hydroxymitraciliatine 3*R*,7*R*,15*S*,20*R* (7), all presenting the *S*- configuration and the *E*- stereochemistry in the double bond on the C-15 methoxy acrylate group (Ramanathan et al., 2021).

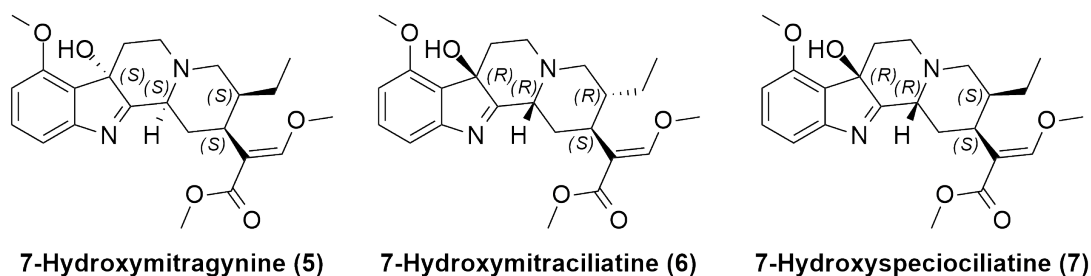


Figure 2. Naturally occurring stereoisomers of 7-hydroxymitragynine. Absolute configurations are indicated.

D. *Methods and Ease of Illicit Manufacturing*

KRATOM

Chemical composition

Most studies of the chemical composition of Kratom are focused on the alkaloids resulting in the isolation of at least 54 alkaloids from the plant (Flores-Bocanegra et al., 2020). Other secondary metabolites like flavonoids, terpenoid saponins, polyphenols, and glycosides have also been isolated or identified in kratom. The main psychoactive components, which are exclusive of *Mitragyna speciosa*, are mitragynine and 7-hydroxymitragynine and are found in the leaves.

The total alkaloid content in dried leaves ranges from 0.5-1.5 %. The most abundant compounds are represented by indoles, mainly of the corynanthe type, which can be found in tetra- or penta-cyclic rings. Hydroxy or methoxy group at C-9, unsaturation at C-3, C-5, or C-18, hydroxylation at C-7, and various configurations at C-3, C-7, and/or C-20 can be encountered in indole and oxindole alkaloids (Flores-Bocanegra et al., 2020).

Mitragynine (1) is the major alkaloid in the kratom plant, reaching up to 66% of the total alkaloid content, and was initially isolated by Field in 1921 (Field, 1921), but only in 1965 its structure was definitely elucidated (Ramanathan et al., 2021, Beckett et al., 2009) and the absolute stereochemistry confirmed by X-ray crystallographic analysis. It is reported that its concentration varies according to plant organ and origin, but also to genetic and morphogenetic factors, plant defense system against pathogenic attacks, light, UV exposure, moisture, temperature, soil microorganisms, soil fertility, salinity, storage conditions (Brown et al., 2017, Tanko et al., 2005).

Mitragynine presents the corynanthe-type skeleton with a tetracyclic tetrahydro- β -carboline, four-cycles with a methoxyl substitution at C-9, an ethyl group at C-20, and a β -methoxy acrylate moiety at C-15 (Tong et al., 2019).

Paynantheine is described as the second major alkaloid accounting for 10% of the total alkaloid content. On average, 7 α -hydroxymitragynine(5) (Figure 2), makes up less than 2% of the alkaloid content (Kruegel et al., 2019).

Oxindole alkaloids are biosynthesized from indole alkaloids through an oxidative rearrangement (Lopes et al., 2019). They are found in *Mitragyna* species and other Rubiaceae species such as *Uncaria* (Heitzman et al., 2005).

The presence of fungi or bacteria can affect the presence and concentration of alkaloids within the plant. For example, *M. speciosa* root cultures infected with *Agrobacterium rhizogenes* generated more mitragynine than not infected plants (Phongprueksapattana et al., 2008). Another reported spirocyclic oxindole is the mitragynine pseudoindoxyl, which is a major transformation product when the fungus *Helminthosporium* sp. feeds upon mitragynine (Yamamoto et al., 1999).

Flavonoids and flavonols have been also identified in *M. speciosa* leaves, including apigenin and its 7-glycosides, along with quercetin and its glycosides (quercitrin, rutin, isoquercitrin, hyperoside, and quercetin-3-galactoside-7-rhamnoside, kaempferol, and its 3-glucoside derivative, and epicatechin). Other phenolic compounds include caffeic acid and chlorogenic acid, 1-O-feruloyl- β -D-glucopyranoside and benzyl- β -D-glucopyranoside (Raffa, 2014, Hinou and Harvala, 1988).

Sitosterol, stigmasterol, and daucosterol are phytosterols that are reported in *M. speciosa* (Phongprueksapattana et al., 2008).

The leaves of *M. speciosa* also contain the monoterpenes 3-oxo- α -ionyl-O- β -D-glucopyranoside and roseoside and secoiridoid glycosides such as vogeloside and epivogeloside (Raffa, 2014).

Adulteration

Preparation of kratom products intended for sale can involve adulteration of the original material. In 2011 it was reported that products were sold in Germany and Sweden

under the name 'Krypton', which were 'enhanced' kratom preparations containing caffeine and synthetic O-desmethyltramadol (ODT)(EMCDDA, 2015, Arndt et al., 2011, Kronstrand et al., 2011).

In 2016 a research article reported concentrations of 7-hydroxymitragynine suspiciously much higher than those found in raw *M. speciosa* leaves in several commercial Kratom products suggesting likely artificial addition of this compound (Lydecker et al., 2016).

Alkaloid extraction

Alkaloids from *Mitragyna* are generally extracted from raw material by methanol, ethanol or 2-propanol), alcohol-chloroform mixture or alcohol–water mixture by maceration, sonication, or the Soxhlet technique. The crude extract undergoes an acid-base purification to yield the alkaloid fraction (Raffa, 2014, Chan et al., 2005).

Other techniques employed are ultrasound-assisted extraction, microwave-assisted extraction, and supercritical carbon-dioxide extraction, which show an increased yield in alkaloids extraction compared to other techniques (Orio et al., 2012).

MITRAGYNINE

Several total syntheses of mitragynine (1) (Figure 1) have been developed (Takayama et al., 1995) (Ma et al., 2009) (Sun and Ma, 2011) (Kerschgens et al., 2012) (Kruegel et al., 2016), but are too complex to be used for economic production of this alkaloid (EMCDDA, 2015). These reported total syntheses require too many steps and provide the final product in very low yields. Moreover, they can be performed only in well-equipped chemical laboratories by well trained personnel. According to the literature records, extraction of the compound seems to be more convenient.

7-HYDROXYMITRAGYNINE

7-hydroxymitragynine can be obtained from mitragynine by a single step chemical reaction. In 2002 Takayama et al. reported that the treatment of mitragynine with lead tetraacetate .and subsequent alkaline hydrolysis led to 7-hydroxy-7*H*-mitragynine in good yield (Takayama et al., 2002).

In 2016 Kruegel et al. reported that mitragynine was easily oxidized to 7-hydroxymitragynine (7-OH) employing the hypervalent iodine species [bis(trifluoroacetoxy)iodo]benzene (PIFA), or by irradiation with visible light in the presence of rose bengal, under air or pure O₂ atmosphere (Kruegel et al., 2016). Interestingly, it was also found that room temperature and sunlight cause the conversion of mitragynine into its 7-hydroxy derivative, with no need for the addition of an external agent, albeit in low yield (8% by NMR) (Kruegel et al., 2016). Therefore, it is conceivable that a similar process occurs in the plant itself, or more likely, in dry leaf material that has been exposed to air for prolonged time, with strongly colored phytochemicals (e.g., porphyrins) serving as a substitute for rose bengal. This phenomenon may account for the observation of 7-OH in

some samples of *Mitragyna speciosa*. In 2019 Kruegel et al. reported that also singlet oxygen and potassium peroxymonosulfate (Oxone) were effective oxidants for the conversion of mitragynine into 7-hydroxymitragynine (Kruegel et al., 2019).

E. Chemical Properties

Melting point

KRATOM

Not applicable.

MITRAGYNINE

It forms white, amorphous crystals that melt at 102-106 °C. The melting point of mitragynine hydrochloric acid salt is 243°C; the picrate melts at 223-224 °C and the acetate at 142 °C (Arndt et al., 2011).

Amorphous crystals of mitragynine show an optical rotation $[\alpha]_D = -126$ (c. 0.66, CHCl₃) (or -128 (c. 1.2, CHCl₃)) (Kerschgens et al., 2012).

7-HYDROXYMITRAGYNINE

No information could be identified.

Amorphous powder of 7-hydroxymitragynine show an optical rotation $[\alpha]_D = +47.9$ (c. 0.55, CHCl₃) (Horie et al., 2005).

Boiling point

KRATOM

Not applicable.

MITRAGYNINE

Mitragynine distils at 230-240 °C at 5 mmHg (EMCDDA, 2015).

7-HYDROXYMITRAGYNINE

No information could be identified.

Solubility

KRATOM

Not applicable.

MITRAGYNINE

Mitragynine is insoluble in water; it is soluble in conventional organic solvents like acetone, acetic acid, alcohols, chloroform and diethyl ether forming fluorescent solutions. The solubility limit of mitragynine was measured in aqueous solution at pH 4 and pH 7 to be 130 and 83 μM , respectively (Kong et al., 2017a). Mitragynine has a LogP (partition coefficient) of 1.73 and a pK_a of 8.11 ± 0.11 (Ramanathan et al., 2015).

7-HYDROXYMITRAGYNINE

No information could be identified.

Stability of kratom alkaloids

Recently, Basiliere and Kerrigan reported the short-term stability of mitragynine, 7-hydroxymitragynine, speciociliatine, speciogynine and paynantheine over a range of pH (2-10) and temperature (4-80 °C) over 8 hours (Basiliere and Kerrigan, 2020b). All of the *Mitragyna* alkaloids studied were acid labile. Hydrolysis of the methyl ester occurs under alkaline conditions to produce 16-carboxymitragynine. 7-hydroxymitragynine is reported to be the most unstable alkaloid studied, with significant drug loss after 8 hours at 40 °C and above. No significant drug losses were observed for mitragynine in aqueous solution (pH 2-10) at 4, 20 or 40 °C. Diastereoisomers of mitragynine (speciociliatine and speciogynine) demonstrated even greater stability (Ponglux et al., 1977, Lersten and Horner, 2011).

F. Identification and Analysis

KRATOM

Botanical identification of Kratom

M. speciosa can be identified macroscopically by examining the leaf, which is elliptic to ovate, with the apex shortly pointed and the base rounded to cordate (Ramanathan et al., 2021). However, macroscopic identification can be misleading as the leaves from plants of the same tribe or genus such as *Uncaria homomalla* and *M. diversifolia* are very similar (Ramanathan et al., 2021) (Brown et al., 2017, Ponglux et al., 1977). Therefore, a chemical analysis can be resolute.

Microscopic identification of eight *Mitragyna* species (but not *M. speciosa*) was reported by examination of calcium oxalate crystals concretions but these studies were based on limited samples (Lersten and Horner, 2011).

In 2007 Sukrong et al. showed that sequences from the nuclear internal transcribed spacer region can be used to differentiate *M. speciosa* from related species by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method (Sukrong et al., 2007).

Recently, a highly specific and selective assay based on DNA bar coding was reported for the detection of kratom products. The assay employs the matK nucleotide signature site as a marker for the discrimination of *M. speciosa* from other mitragyna species (Jaipaew et al., 2018).

In 2021, a DNA bar coding combined with high-resolution melting (Bar-HRM) analysis method was developed to differentiate *M. speciosa* from other related *Mitragyna* species. The authors proposed the Bar-HRM analysis as a simple method for the investigation of *M. speciosa* to be used in routine forensic analysis (Tungphatthong et al., 2021).

Chemical analysis of kratom

Numerous analytical methods have been reported in the literature for the identification and quantification of kratom alkaloids, particularly mitragynine, in a wide range of samples, including commercial samples, raw plant material and biological specimens. Commercial standards of mitragynine and its stereoisomers speciogynine, mitraciliatine, speciociliatine, its hydroxylate derivative 7-hydroxymitragynine, as well as deuterated mitragynine and 7-hydroxymitragynine, are available. Some other indole and oxindole kratom alkaloids are sold as analytical standards, although Flores-Bocanegra et al. reported that in some cases pure commercial standards turned out to be either mixtures or even a completely different compound (Flores-Bocanegra et al., 2020).

Chromatographic methods, and in particular liquid chromatography, are the most commonly employed for the analysis of *M. speciosa* alkaloids. A detailed description of the analytical methods is provided below according to the technique chosen.

Thin Layer chromatography (TLC)

Kratom alkaloids can be separated by TLC on silica gel plates and detected under a UV lamp (254 nm). A mobile phase composed of hexane/ethyl acetate/25% ammonia solution (30:15:1, v/v/v) provides an R_f value of mitragynine of 0.49 (Kowalczyk et al., 2013). Spraying with either modified Ehrlich's reagent or ferric chloride-perchloric acid reagent, mitragynine can be detected as purple or gray-to-brown spots, respectively (Lydecker et al., 2016).

Gas chromatography (GC)

The first GC method for the analysis of mitragynine in kratom was published in 2005 (Orio et al., 2012), but the identification of mitragynine was given only by comparison of experimental mass spectra with library spectra.

Philipp et al. in 2011 developed a GC-MS method for the analysis of kratom and/or Krypton in urine by trimethylsilylation to increase the volatility of the alkaloids (Philipp et al., 2011a).

Cornara et al. in 2013 described a GC-MS method for the analysis of underivatized mitragynine and other alkaloids in kratom (Cornara et al., 2013).

Wang et al. in 2014 compared three chromatographic methods coupled to two detection systems, GC with MS, supercritical fluid chromatography with diode array detection (DAD), and HPLC with MS and DAD, for the analysis of mitragynine and other structurally related alkaloids in *M. speciosa* plants (Wang et al., 2014). The authors concluded that the GC method was unable to resolve the two diastereoisomers mitragynine and speciociliatine, which also give identical electron impact mass spectra. This issue could be overcome only by applying derivatization. Moreover, there is the limitation of the temperature range available for method optimization.

Mohd et al. published a GC-MS method for the determination of mitragynine in three Malaysian *M. speciosa* samples employing ultrasonic assisted extraction (UAE) (Sanagi et al., 2013).

Basilieri et al. suggested that GC methods lacked overall sensitivity (limit of detection (LOD) of about 50 ng/mL), thus being unable to quantify the alkaloids in biological specimens (Basilieri et al., 2018).

Liquid chromatography (LC)

LC-UV

HPLC and UHPLC (ultrahigh) methods have proven to provide the highest accuracy in the discrimination of structurally similar kratom alkaloids (Ramanathan et al., 2021).

An HPLC-DAD method was developed to identify and quantify mitragynine, along with caffeine, codeine, chlorpheniramine and phenylephrine in a “kratom cocktail,” a drink prepared by mixing boiled kratom leaves, carbonated cola beverages, antitussive syrup, coffee, and codeine (Chittrakarn et al., 2012).

Parthasarathy et al. reported a HPLC-DAD method to quantify mitragynine from raw material (Parthasarathy et al., 2013).

Mudge et al. reported in 2017 an HPLC-UV validated method for the qualitative and quantitative analysis of mitragynine and 7 α -hydroxymitragynine in solid and liquid commercial kratom products (Mudge and Brown, 2017).

Parthasarathy et al. reported in 2010 a solid phase extraction method for HPLC-UV determination of mitragynine in rat plasma. The method had limit of quantification (LOQ) of 50 ng/mL (Parthasarathy et al., 2010).

Neng et al. developed an extraction method of mitragynine from human urine using a bar adsorptive microextraction, consisting of a modified N-vinylpyrrolidone polymer sorbent phase combined with liquid desorption and followed by analysis by HPLC-DAD (BA μ E-LD/HPLC-DAD) (Neng et al., 2015).

LC-MS

Liquid chromatography-based methods are the most widely employed for the determination of kratom alkaloids as they allow for a good resolution of mitragynine isomers and have a high sensitivity, which is a key factor for the qualitative and quantitative determination of trace amounts of such compounds found in biological specimens. Since metabolites of mitragynine are not yet commercially available, the assessment of kratom use in forensic toxicology specimens is currently evaluated by the analysis of the parent drug and related alkaloids. As reported in a study of mitragynine concentrations in urine from fifty recreational kratom users, values covered a broad dynamic range (1-50,000 ng/mL) (Le et al., 2012). For forensic investigations, it is important to have analytical methods capable of detecting low ng/mL concentrations.

LC-MS methods were developed for the simultaneous determination of mitragynine, 7-hydroxymitragynine, speciogynine, speciociliatine, and paynantheine in both raw material and commercial kratom products (Kikura-Hanajiri et al., 2009). Some methods are able to reach very high sensitivities up to 0.02 ng/mL and 0.1 ng/mL for the LOD and LOQ of mitragynine, respectively (Lu et al., 2009).

The LC technique was also coupled to low- and high-resolution mass spectrometry (LC-HRMS) to identify phase I and II metabolites of speciogynine in rat urine after the administration of a high dose of the pure alkaloid and in human urine after kratom use (Philipp et al., 2010a). The same method was applied to paynantheine (Philipp et al., 2010b), speciociliatine (Philipp et al., 2011b), mitraciliatine and isopaynantheine (Philipp et al., 2011c) and their metabolites in rat urine after administration of the pure alkaloids showing that they matched the metabolites detected in the urine of kratom users.

An LC-MS/MS method was able to detect O-desmethyltramadol besides kratom alkaloids in urine of a woman after consumption of "Krypton", a mixture of kratom and O-desmethyltramadol (Arndt et al., 2011).

Mitragynine was also detected in post-mortem urine and blood samples by LC-MS/MS (Holler et al., 2011) after hydrolysis with glucuronidase and sulfatase and extraction with n-butyl chloride prior to analysis. The method was also applied to other specimens including liver, vitreous humor, kidney, spleen, lung, bile, and heart,) with the latter being the only specimen in which mitragynine was not detected.

A method using solid phase extraction (SPE) and LC-MS/MS to detect and quantify mitragynine, 16-carboxy mitragynine, and 9-O-demethyl mitragynine in human urine was also developed (Lee et al., 2018).

Recently, a simultaneous quantification in marketed products of 10 kratom alkaloids (corynantheidine, corynoxine, corynoxine B, 7-hydroxymitragynine, isocorynantheidine, mitragynine, mitraphylline, paynantheine, speciociliatine, and speciogynine) using an UHPLC MS-MS method was reported by the Avery group (Sharma et al., 2019). The LOQ was 1 ng/ml. The method was applied to the quantification of kratom alkaloids in alkaloid-rich fractions, ethanolic extracts, lyophilized teas, and commercial products. The most abundant alkaloids were mitragynine (0.7-38.7% w/w), paynantheine (0.3-12.8%), speciociliatine (0.4-12.3%), and speciogynine (0.1-5.3%). Minor kratom alkaloids like corynantheidine, corynoxine, corynoxine B, 7-hydroxymitragynine, isocorynantheidine were found in the range 0.01%-2.8% (w/w). However, mitraphylline was below the LOQ in all analyses. The

same group also developed an HPLC method for the quantification of mitragynine in kratom leaf extracts and a multiple reaction mode based UPLC-MS/MS method for the quantification of the same alkaloid in rat plasma (Avery et al., 2019).

Speciociliatine and speciogynine were investigated as alternative biomarkers of kratom use in urine, as they often exceeded the concentration of mitragynine in unhydrolyzed urine (Basiliere and Kerrigan, 2020a).

Recently, a method for the detection of mitragynine and 7-hydroxymitragynine with LC-MS/MS in hair samples with LOQs of 4 pg/mg and 30 pg/mg, respectively, was developed (Meier et al., 2020).

Supercritical fluid chromatography (SFC)

Three chromatographic techniques, GC-MS, SFC-DAD, and LC coupled either to DAD or MS, were compared for the analysis of the indole alkaloids paynantheine, 3-isopaynantheine, mitragynine, speciogynine, and speciociliatine, and the oxindole alkaloids corynoxine and corynoxine B in *M. speciosa* plants (Wang et al., 2014). LC and SFC were able to resolve the major components with slightly different elution orders. On the other hand, the GC method failed to resolve the diastereoisomers mitragynine and speciociliatine.

Capillary electrophoresis (CE)

Non-aqueous capillary electrophoresis (NACE) interfaced to an MS detector was successfully employed to separate a large number of diastereomeric compounds in alkaloid mixtures from a plant extract of *M. speciosa* (Posch et al., 2012). In this separation technique, background electrolytes often consist of a mixture of methanol and acetonitrile (ACN) with soluble ammonium salts added as electrolyte. Posch et al. used a mixture of glacial acetic acid and can, thus creating an acidic background electrolyte with a very low dielectric constant. The addition of ammonium formate as electrolyte and variation of the solvent ratio led to significant changes in selectivity and resolution necessary for the separation of structurally closely related indole alkaloids including diastereomers upon (Posch et al., 2012).

DART

A direct analysis in real time-mass spectrometry (DART-MS) method was developed by Lesiak et al. for the rapid identification of *M. speciosa* plant material and discrimination from other plants (Lesiak et al., 2014). Moreover, *M. speciosa* plant varieties were also analyzed and classified according to their chemical profile.

Fowble et al. developed DART-HRMS method for the quantification of mitragynine and 7-hydroxymitragynine in 16 online commercially available kratom products (Fowble and Musah, 2019). The linear range was 5-100 $\mu\text{g/mL}$, the LOQ was 5 $\mu\text{g/mL}$, and the mitragynine concentrations in these samples ranged from 2.76 to 20.05 mg/g of dried plant material. The advantage of using a DART system lies in the straightforward analysis of raw plant material as such with no sample preparation steps (Fowble and Musah, 2019, Lesiak et al., 2014).

Ion mobility spectrometry (IMS)

Fuenffinger et al. developed an IMS method for the quantification of mitragynine in 15 commercial samples and compared the results with those obtained by an LC-MS/MS method (Fuenffinger et al., 2017). The LOD was 0.5 ng. Mitragynine was detected in 14 of 15 samples using LC-MS/MS and 13 of 15 samples using IMS as in one sample the compound was below the LOD.

Raman and portable devices

Surface-enhanced Raman spectroscopy (SERS) was used to detect mitragynine in *M. speciosa* samples Lanzarotta et al. (Lanzarotta et al., 2020). The advantage of the method is of the possibility to be applied by non-expert users. Over 100 samples and blanks were examined in duplicate using five identical handheld Raman spectrometers with the same method, which provided a false-positive rate of 2.1% and a false-negative rate of 0.7%. The LOD of mitragynine was 342 ng/mL (ppb). The method is ideal for preliminary screening test of mitragynine that can be then confirmed by other more time-consuming laboratory-based techniques.

In another record, DART with thermal desorption MS (DART-TD-MS), hand-held MS, portable ion mobility spectrometry (IMS), and portable Fourier-transform IR spectroscopy (FT-IR) were tested as field screening techniques for the detection of mitragynine in food and drug products and the results were compared to those obtained with laboratory techniques like LC-MS, HPLC-UV, and GC-MS (Voelker et al., 2021). The methods developed were applied to 96 kratom products, including capsules, bulk powder, and bulk plant material. The results suggested that the four portable devices provided a rapid detection of mitragynine in chloroform extracts and/or analysis of solid sample material in kratom matrices. The DART-TD-MS and IMS can be easily employed for the initial screening of materials because of very short analysis time and absence of sample preparation. Hand-held MS exhibited the highest false negative rate (6%). FT-IR, as well as the hand-held MS, requires extraction of the sample.

Immunological methods

Although chromatographic techniques have the advantages of good sensitivity, the separation step limits their routine use. Therefore, other screening and detection methods have been developed in recent years. For example, immunoassays are worldwide used for rapid screening or detection drugs in kratom preparations and biological fluids with the advantage of good sensitivity, simplicity and convenience (Schütz et al., 2006).

An issue that can be encountered with immunological assays is the potential cross-reactivity of the developed antibody against a specific kratom alkaloid with other alkaloids present in a sample (Limsuwanchote et al., 2017) (Lee et al., 2020).

An electrochemical immunosensor for the sensitive and rapid detection of mitragynine, using a modifier for the sensor based on multiwalled carbon nanotubes/chitosan nanocomposite was also developed (Mustafa et al., 2021). The detection of mitragynine resulted from an indirect competitive assay with 3,3',5,5'-tetramethylbenzidine (TMB), which is the substrate in the enzymatic reaction of HRP-modified secondary antibody. The electrochemical immunosensor showed higher sensitivity

(10-fold) compared to conventional ELISA with a LOD of 0.018 µg/mL and a LOQ of 0.06 µg/mL.

MITRAGYNINE

Besides the methods developed for the analysis of mitragynine in kratom samples, the pure synthetic compound was obtained and characterized by NMR (Takayama et al., 1995, Ma et al., 2009, Sun and Ma, 2011, Kerschgens et al., 2012, Kruegel et al., 2016), HRMS (Sun and Ma, 2011), [α]D (Takayama et al., 1995, Kruegel et al., 2016) and elemental analysis (Ma et al., 2009).

7-HYDROXYMITRAGYNINE

Besides the methods developed for the analysis of 7-hydroxymitragynine in kratom samples, the pure synthetic compound was obtained and analysed by NMR (Kruegel et al., 2016, Takayama et al., 2002) and both EI-MS and HRMS (Takayama et al., 2002).

3. Ease of Convertibility Into Controlled Substances

KRATOM

It is not known from the literature that kratom can be converted into a controlled substance.

MITRAGYNINE

It is not known from the literature that mitragynine can be converted into a controlled substance. As reported above (*Section 2. Chemistry, subsection D. Methods and Ease of Illicit Manufacturing*), mitragynine can be converted into the bioactive 7-hydroxymitragynine in only one step (Kruegel et al., 2019, Kruegel et al., 2016, Takayama et al., 2002). However, 7-hydroxymitragynine is not listed as a controlled substance.

7-HYDROXYMITRAGYNINE

It is not known from the literature that 7-hydroxymitragynine can be converted into a controlled substance.

4. General Pharmacology

Kratom is the common term for *Mitragyna speciosa*, a tree native to Southeast Asia, including Myanmar, Thailand, Malaysia, Indonesia, New Guinea, and the Philippines. The indigenous population has used kratom leaves and derived products for centuries as an herbal medicine to treat pain, cough, diabetes, diarrhea, fever, and as a wound poultice, to enhance sociability and sexual desire, and to increase energy and decrease fatigue (especially among manual workers) (Singh et al., 2016). More recently, kratom has been used as an opioid substitute and to treat opioid withdrawal. Lower doses (1-5 g p.o. of plant material) reportedly have stimulant-like effects, while higher doses (concentrated products such as kratom extracts or >5 g p.o. of plant material) have opioid-like effects (Toce et al., 2018). Kratom use has spread to the United States and Western Europe over the past two

decades, chiefly to self-medicate pain and opioid withdrawal and as a substitute for opioids (Singh et al., 2016).

Kratom contains more than 50 different alkaloids but only two indole alkaloids, mitragynine and its active metabolite 7-hydroxymitragynine (Kruegel et al., 2019), have been well characterized pharmacologically (Todd et al., 2020; Zhou et al., 2021). A third alkaloid, mitragynine pseudoindoxyl, is not found in the plant but is a metabolite of 7-hydroxymitragynine and active *in vitro* at the mu-opioid receptor (Kamble et al., 2020). Mitragynine comprises up to two-thirds of the total alkaloid content and is considered primarily responsible for the pharmacological actions of kratom. 7-Hydroxymitragynine comprises 1% or less of kratom alkaloids in the leaf, but is often present in higher concentration in processed kratom products sold commercially (Lydeker et al., 2016). Kratom grown experimentally in the US may have a lower mitragynine content than kratom grown in Thailand (Leon et al., 2009).

A. Routes of administration and dosage

Kratom is almost always taken orally in several forms. In Southeast Asia, typical formulations include chewing raw leaves, ingesting powdered leaves, or using leaves or leaf-extract to brew tea or create a decoction (boiling the leaves for several hours) (Singh et al., 2016; Singh et al., 2017). Kratom decoction is often mixed with another beverage (e.g., cola, cough syrup) to create a kratom “cocktail,” in part to hide its bitter taste (Singh et al., 2016; Singh et al., 2017). In the United States and Western Europe, kratom is commonly taken as a powder dissolved in a beverage or in a capsule or tablet (Garcia-Romeu et al., 2020; Grundmann, 2017; Singh et al., 2016). Mitragynine and 7-hydroxymitragynine have been found in resins and liquids sold online for use in electronic drug delivery devices (so-called “e-cigarettes”) (Pearce et al., 2020).

In the absence of accurate labeling of kratom products, it is impossible to know the actual doses of kratom alkaloids ingested by kratom users. In Southeast Asia, surveys of convenience samples of kratom users suggest that a typical daily dose of liquid formulations (tea, decoction) is 3-6 glasses/day, containing an estimated 200-400 mg of mitragynine (Ahmad and Aziz, 2012; Saref et al., 2019). In the US, surveys of convenience samples of kratom users suggest that a typical daily dose of powder formulations is 2-6 g/day, although heavy users may ingest up to 20 g/day (Garcia-Romeu et al., 2020; Grundmann, 2017).

B. Pharmacokinetics

a. Animal studies

Oral mitragynine (20-50 mg/kg) in rats has a mean T_{max} of 1.3-4.5 hours, mean C_{max} of 400-700 ng/mL, and mean half-life of 3.3-9.4 hours (Avery et al., 2019; Ramachandram et al., 2020; Ya et al., 2019). Mean oral bioavailability was 17% and 3% (Avery et al., 2019; Parthasarathy et al. 2010). Oral dosing of rats with lyophilized kratom tea or organic extract of kratom tea (equivalent of 20 mg/kg mitragynine) generated T_{max} of 0.3 and 1.0 hours, respectively, C_{max} of 0.55 and 0.66 ng/mL, respectively, and oral bioavailability of 25.1% and 31.2%, respectively (compared to 17.0% with pure mitragynine) (Avery et al., 2019).

Oral mitragynine (5 mg/kg) in beagle dogs has a T_{max} of 0.3 (± 0.1) hours, C_{max} of 278 (± 47.4) ng/mL, half-life of 8.7 (± 0.2) hours, and bioavailability of 69.6% (Maxwell et al., 2020).

A rat study found that intravenous mitragynine readily crosses the blood-brain barrier, with a T_{max} and half-life comparable to that in plasma (Kong et al., 2017b). We are not aware of any human studies regarding the blood-brain barrier.

b. Human studies

There are two published human studies of oral kratom pharmacokinetics, both in young adult men living in Southeast Asia who used kratom daily for at least 0.5 years at the time of the study. One study gave kratom tea (60 mL containing 6.25-11.5 mg mitragynine) daily for 7 days to 10 Thai men (mean [SD] body weight 77.3 [14.8] kg) (Trakulsrichai et al., 2015). Blood and urine samples were collected for 24 hours after a loading dose (equivalent of 6.25-23 mg mitragynine) given on the eighth day. Mitragynine mean (SD) T_{max} was 0.83 (0.35) hours and elimination half-life 23.24 (16.07) hours. The C_{max} varied linearly ($R^2 = 0.677$) with the loading dose: 18-30 ng/mL after 6.25 mg to 50-100 ng/mL after 20-23 mg. The second study gave 26 Malaysian men a single mitragynine dose of 1.6 mg/kg in the form of a kratom decoction containing 0.4-0.5 mg/mL mitragynine (Dr. Marek Chawarski, personal communication). Mitragynine mean (SD) T_{max} was 2.0 (0.8) hours (range 1-3 hours); C_{max} was 1884 (1056) ng/mL (range 829-5034 ng/mL) (Vicknasingam et al., 2020; Dr. Marek Chawarski, personal communication).

There are currently no human data on the oral bioavailability of mitragynine or 7-OH-mitragynine, either alone or as part of a kratom product. Given this lack of knowledge, and the known variability in oral bioavailability between rodents and beagle dogs (see above), it is impossible to accurately extrapolate to humans from the animal dosing of kratom and kratom alkaloids.

The overall effect of mitragynine on human liver cytochrome P450 activity remains unclear. Mitragynine inhibits three human liver cytochrome P450 enzymes (CYP2C9, CYP2D6, CYP3A) in human liver cells *in vitro* at 1 μ M concentration (Todd et al. 2020). 7-Hydroxymitragynine is a weaker inhibitor than mitragynine. A separate study found that mitragynine (1-25 μ M) produced concentration-dependent increases in mRNA and protein expression and *in vitro* enzyme activity of CYP1A2, CYP2D6, and CYP3A4 in human liver cells *in vitro* (Lim et al., 2013). These *in vitro* findings suggest the possibility of clinically significant kratom-drug pharmacokinetic interactions with commonly used medications that are metabolized by these liver cytochromes, such as warfarin (CYP2C9), desipramine and dextromethorphan (CYP2D6), and benzodiazepines (CYP3A) (US Food and Drug Administration, 2020).

C. Pharmacodynamics

a. Animal studies

Mitragynine, 7-hydroxymitragynine, and mitragynine pseudoindoxyl are partial agonists at the human mu-opioid receptor, activating the G-protein-coupled intracellular

signaling –pathway while having little or no effect on the beta-arrestin pathway (Gutridge et al., 2020; Kruegel et al., 2016; Todd et al., 2020; Varadi et al., 2016; Zhou et al., 2021). This so-called mu-opioid receptor agonist bias has been proposed as conferring differential efficacy on mu-opioid receptor ligands. Ligands that preferentially activate the G-protein-coupled intracellular signaling pathway should have greater efficacy in producing analgesia and lesser efficacy in producing respiratory depression and physical dependence than ligands preferentially activating the beta-arrestin pathway (De Neve et al., 2021; Faouzi et al., 2020). A mouse study found that mitragynine pseudoindoxyl, at subcutaneous doses equipotent with morphine for analgesia, was significantly less potent than morphine in generating tolerance or withdrawal, slowing gastrointestinal transit, causing respiratory depression, or rewarding behavior (Varadi et al., 2016). However, human studies with an experimental mu-opioid receptor biased analgesic (not kratom-derived) find limited evidence for significantly reduced adverse effects compared to standard opioid analgesics (Tan & Habib, 2021).

7-Hydroxymitragynine has a 5-23-fold greater affinity than does mitragynine at the mu-opioid receptor (depending on the binding assay used) (Obeng et al., 2020; Obeng et al., 2021; Todd et al., 2020; Varadi et al., 2016). Morphine has 8-10-fold greater affinity than does 7-OH-mitragynine (Obeng et al., 2021; Todd et al., 2020; Varadi et al., 2016). Mu-opioid receptor activation is the mechanism considered responsible for the majority of pharmacodynamic effects of kratom and its alkaloids that are observed in rodents and humans. Mitragynine and 7-hydroxmitragynine are also competitive antagonists at the human kappa- and delta-opioid receptors (Kruegel et al., 2016), with less affinity than at the mu-opioid receptor (Obeng et al., 2021; Yue et al., 2018).

7-OH mitragynine has 5-20-fold greater efficacy than does mitragynine for activating the β -arrestin pathway (i.e., intrinsic activity) at the mu-opioid receptor (Obeng et al., 2021; Todd et al., 2020; Varadi et al., 2016). Morphine has 3-fold greater intrinsic activity at the mu-opioid receptor than does 7-)H-mitragynine ((Obeng et al., 2021; Todd et al., 2020),

Mitragynine, but not 7-hydroxymitragynine, binds to alpha1- and alpha2-adrenergic receptors and serotonin-1A and -2A receptors (Ellis et al., 2020; Obeng et al., 2020). Mitragynine binds with low affinity to dopamine-D1 receptors on rat striatal membranes and not at all to dopamine-D2 receptors (Stolt et al., 2014). The functional significance of such binding remains unclear.

Kratom extracts, mitragynine, and 7-hydroxymitragynine have a variety of behavioral effects in rodents. Some effects are not observed consistently across studies, perhaps because of methodological differences in dose, type of kratom extract, route of administration, and timing of data collection (e.g., see motor activity below). Few studies evaluate a broad range of doses, so might miss effects at lower or higher doses or non-linear dose-response relationships. The most consistently observed effects are opioid-like (Prevete et al., 2021): analgesia (Chin et al., 2018), suppression of opioid withdrawal (Wilson et al., 2021), and inhibition of gastrointestinal transit (Avery et al., 2019).

Kratom extracts, mitragynine, 7-hydroxymitragynine, and mitragynine pseudoindoxyl significantly reduce acute mechanical or thermal pain in rats and mice by the intracerebroventricular, intraperitoneal, subcutaneous, or oral route of administration (Chin et al., 2018; Wilson et al., 2020). The analgesic effect is blocked by pretreatment with mu-opioid receptor antagonists (Chin et al., 2018) and does not occur in knock-out mice lacking the mu-opioid receptor (Bhowmik et al., 2021; Stott et al., 2014; Wilson et al., 2020), suggesting a mu-opioid receptor mechanism of action. Repeated dosing generates tolerance to the analgesic effect and there is cross-tolerance among mitragynine, 7-hydroxymitragynine, and morphine (Chin et al., 2018). The relative analgesic potency of kratom alkaloids vs. conventional opioids remains uncertain because very few studies have compared the two using the same route of administration over a range of doses to establish equipotent doses. A rat study found that 100 mg/kg oral mitragynine had the same analgesic effect as 6 mg/kg oral oxycodone (Carpenter et al., 2016).

Kratom extracts, mitragynine, and 7-hydroxymitragynine suppress naloxone-precipitated opioid withdrawal in rodents by the intraperitoneal or oral route of administration (Cheaha et al., 2017; Harun et al., 2020; Wilson et al., 2020; Wilson et al., 2021).

Kratom extracts and mitragynine have inconsistent effects on motor activity in rodents. In several mouse studies, kratom extract decreased (mitragynine 0.5 mg/kg i.p. or p.o.) (Stolt et al., 2014), increased (mitragynine 7.4 mg/kg p.o.) (Wilson et al., 2020), or had no effect (50-200mg/kg p.o. methanolic extract or 5-20 mg/kg p.o. alkaloid extract) (Reanmongkol et al., 2007) on motor activity. In another study, mitragynine (30 mg/kg i.p.) had no effect (Matsumoto et al., 1997). In three rat studies, kratom alkaloid extract (60 mg/kg p.o.) had no effect (Cheaha et al., 2015), while mitragynine had no effect on (1-10 mg/kg i.p.) (Suhaimi et al., 2021) or increased (30 mg/kg i.p.) (Foss et al., 2020) motor activity. 7-Hydroxymitragynine (3 mg/kg i.p.) increased motor activity in male and female mice (Gutridge et al., 2020).

Kratom extracts and mitragynine have a variety of non-opioid-like behavioral effects in rodents (Prevete et al., 2021). They reduce immobility in the forced swim test and tail suspension test, which are considered rodent models of anti-depressant action (Buckhalter et al., 2021; Idayu et al., 2011). Kratom extract significantly influences behavior in several mouse models of anti-psychotic action, including apomorphine-induced climbing behavior, haloperidol-induced catalepsy, and ketamine-induced social withdrawal (Vijeepanam et al., 2016). Kratom extracts in mice and rats reduce alcohol self-administration, alcohol reinforcement (conditioned place preference), alcohol-induced increase in dopamine concentration in the nucleus accumbens, and alcohol withdrawal (Gutridge et al., 2020; Kumarnsit et al., 2007; Vijeepallam et al., 2019). In rats, mitragynine (10-30 mg/kg i.p.) attenuates the acquisition and expression of morphine conditioned place preference (Meepong et al., 2019) and reduces heroin self-administration but not methamphetamine self-administration (0.1-3.0 mg/kg i.p.) (Yue et al., 2018).

b. Human studies

In an observational study done in Britain in the early 1930's, five adult men given oral mitragynine acetate (50 mg once, or twice separated by two hours) or kratom (0.65 g or 1.3 g of powdered leaves) had reduced heat sensitivity and skin electrical resistance and dilatation of skin blood vessels (Grewal, 1932).

In a recent controlled clinical trial involving 26 Malaysian young adult men who were daily kratom users, a single oral dose of 1.6 mg/kg mitragynine (as a kratom decoction containing 0.4-0.5 mg/mL mitragynine [Dr. Marek Chawarski, personal communication]) doubled pain tolerance in the cold pressor test about one hour after ingestion (Vicknasingam et al., 2020). There was no change in pain threshold at two hours after ingestion.

5. Toxicology

a. Animal studies

In mice, the oral acute LD50 is 547.7 mg/kg or 477.1 mg/kg for mitragynine (Sabetghadam et al., 2013a; Smith et al., 2019), 173.2 mg/kg or 591.6 mg/kg for a kratom alkaloid extract (20-22% mitragynine) (Reanmongkol et al., 2007; Sabetghadam et al., 2013a) and 4.9 g/kg for kratom methanolic extract (Reanmongkol et al., 2007). Death is preceded by tremor, paralysis, apnea, and seizures, usually within one hour of administration (Reanmongkol et al., 2007; Sabetghadam et al., 2013a). 7-Hydroxymitragynine was not lethal at the highest dose administered (50 mg/kg), but respiratory depression and seizures were observed at the higher doses (Smith et al., 2019). The intravenous acute LD50 is 27.8 mg/kg for mitragynine and 24.7 mg/kg for 7-hydroxymitragynine (Smith et al., 2019). Death occurred by respiratory depression, usually within 10 minutes of administration. For comparison, the oral LD50 of morphine in mice is 600 mg/kg (Pfizer, 2017).

In rats, the oral LD50 was 4.9 g/kg for kratom methanolic extract and 173.2 mg/kg for kratom alkaloid extract (Reanmongkol et al., 2007). Mitragynine is acutely lethal at 100 mg/kg i.p., but not at 56 mg/kg i.p. (Obeng et al., 2021) and shows no toxicity at single oral doses up to 806 mg/kg (Macko et al., 1972). For comparison, the oral LD50 of morphine in rats is 461 mg/kg (Pfizer, 2017). Repeated oral dosing with 5 mg/kg/day or 50 mg/kg/day five days/week for 6 weeks or 1 mg/kg/day or 10 mg/kg/day for 4 weeks produces no toxicity (Macko et al., 1972; Sabetghadam et al., 2013b). Repeated oral dosing with 100 mg/kg/day for 4 weeks produces no death, tremor, or seizures, but decreases food intake and body weight and increases liver transaminase and blood urea nitrogen levels in female rats and reduces red and white blood cell counts in both female and male rats (Sabetghadam et al., 2013b). Histopathological examination of internal organs shows abnormalities in the liver and neuronal damage (but no axonal changes) in the medulla, hippocampus, frontal cortex, and cerebellum. There were no inflammatory changes or hemorrhage. A single oral dose of kratom methanolic extract (up to 1000 mg/kg) produces no acute toxicity (Harizal et al., 2010). Repeated oral dosing with a kratom methanolic extract (100 mg/kg, 500 mg/kg, or 1000 mg/kg daily for 14 days) produces a 10-20% increase in systolic and diastolic blood pressure and increased blood concentrations of urea nitrogen, creatinine, liver

transaminases, cholesterol, and triglycerides, with no significant changes in food and water intake, body weight, weight of internal organs, or blood count (Harizal et al., 2010). The highest dose produced liver damage (sinusoidal congestion, fatty changes, necrosis), but no changes in kidney, lung, or brain.

In dogs, mitragynine at 80 mg/kg orally or 4.6 mg/kg i.v. produces no acute effects; 9.2 mg/kg i.v. produces slowed respiration and ataxia, 31.8 mg/kg i.v. produces respiratory depression and seizures (Macko et al., 1972). Repeated oral dosing with mitragynine (5 mg/kg/day or 20 mg/kg/day 6 days/week for 3 weeks) produces no toxicity (Macko et al., 1972). Increasing the dose to 40 mg/kg/day for weeks 4-7 produces decreased white blood cells, atypical lymphocytes, bone marrow hyperplasia, hyperplastic lymph nodes, and increased diffuse sinusoidal cellularity in the liver. In anesthetized dogs, mitragynine (cumulative dose of 18.5 mg/kg i.v.) has no significant effect on mean arterial blood pressure (Macko et al., 1972).

In cats, mitragynine (9.2-46.0 mg/kg i.p.) produces dose-dependent mydriasis and restlessness (Macko et al., 1972). In anesthetized cats, i.v. mitragynine was lethal at 4.6 or 9.2 mg/kg (Macko et al., 1972).

Both acute mitragynine (1, 5, or 10 mg/kg i.p.) and chronic mitragynine (1, 5, or 10 mg/kg i.p. daily for 28 days) impair the acquisition, consolidation, and retrieval of short-term memory in rats (Yusoff et al., 2014). These effects were comparable to those produced by morphine (5 mg/kg i.p.).

Kratom alkaloid extract reduces food and water intake acutely at 45 and 50 mg/kg i.p. but not 15 or 30 mg/kg i.p.; 40 mg/kg/day i.p. over 60 days also produced weight loss (Kumarnsit et al., 2006).

Kratom extract has no significant effect on sleep in mice (Reanmongkol et al., 2007) or rats (Cheaha et al., 2015).

Mitragynine (1, 5, or 10 mg/kg i.p.) acutely decreased EEG delta band power in the hippocampus and delta and theta activity in the frontal cortex of freely moving rats in one study (Yusoff et al., 2014) but had no effect in another study (Suhaimi et al., 2021). Chronic mitragynine (1, 5, 10 mg/kg/day i.p. for 60 days) significantly increased delta power in the cortex and decreased alpha power in the cortex and delta power in the hippocampus (Suhaimi et al., 2021). Kratom alkaloid extract (about 60% mitragynine) (80 mg/kg orally) has no effect on local field potentials in the mouse nucleus accumbens (Cheaha et al., 2017).

6. Adverse Reactions in Humans

No clinically significant adverse events or clinical laboratory or vital signs abnormalities were noted in 36 adult men who used kratom regularly in Southeast Asia and received either a single oral dose of a kratom decoction (mitragynine dose 1.6 mg/kg [Dr. Marek Chawarski, personal communication]) (Vicknasingam et al., 2020) or 8 daily doses of kratom tea (6.25-23 mg mitragynine) (Trakulsrichai et al., 2015) as part of a clinical trial. All participants in the kratom tea trial reported transient tongue numbness after drinking the kratom tea (Trakulsrichai et al., 2015).

In an observational study done in the early 1930's in Britain, five adult men given oral mitragynine acetate (50 mg once, or twice separated by two hours) or kratom (0.65 g or 1.3

g of powdered leaves) reported transient, mild side-effects at the higher doses, including giddiness, nystagmus, pupillary constriction, muscle tenseness, hand/tongue tremor, stomach irritation, nausea, sleepiness, and impaired motor coordination (Grewal, 1932).

At least 3,859 cases of non-lethal adverse reactions associated with kratom were reported to US poison control centers (National Poison Data System [NPDS]) between 2010 and 2019 (Anwar et al., 2016; Cumpston et al., 2018; Graves et al., 2021; Post et al., 2019). The number of annual cases increased from 26 in 2010 to 100 in 2013, 263 in 2015, 568 in 2017, and 1218 in 2019 (Anwar et al., 2016; Graves et al., 2021). Among the 3,484 cases reported from 2014-2019, the majority involved men (68.2%) and only kratom (63.0%) (Graves et al., 2021). Almost all cases were 18-59 years old (95.4%); 1.7% were 60-69 years old and 0.9% were 70 years or older. Among reports with information available, the route of administration was oral in 93.3%; kratom formulations were tablet or capsule 50.0%, powder or granules 19.1%, liquid 9.4%, and aerosol or topical 21.3%. Among the 2196 cases with kratom as the only substance mentioned, 0.8% were considered as involving major clinical effects (including death); 39.5% involved moderate effects, 26.6% involved minor effects, and 13.5% involved minimal or no effects. The major clinical toxicities were neuropsychiatric (agitation, confusion, sedation, hallucinations, tremor, seizure, coma) 75.4%, cardiovascular (tachycardia hypertension) 44.5%, gastrointestinal (abdominal pain, nausea, vomiting) 25.2%, and respiratory (respiratory depression) 12.1%. Among the 1174 cases involving only kratom that were reported to the NPDS from 2011-2017, the commonest individual clinical manifestations were agitation or irritability (22.9%), tachycardia (21.4%), nausea (14.6%), drowsiness or lethargy (14.3%), vomiting (13.2%), hypertension (10.1%), confusion (10.9%), and seizure (9.6%) (Post et al, 2019). Life-threatening conditions were rare: coma (3.6%), cardiac arrest (0.4%), respiratory arrest (0.5%), renal failure (0.5%).

A comparison of kratom-associated cases reported from 2010 to 2017 to the US NPDS (760 cases) and the Ramathibodi Poison Center in Thailand (168 cases) found that Thailand had a significantly higher proportion of cases with other substances present (64.8%) than did the US (37.4%) (odds ratio 3.10, 95% CI 2.15-4.47), with opioids and benzodiazepines being the commonest second substance in both countries (Davidson et al., 2021). Common clinical manifestations in both countries included agitation and irritability, tachycardia, and drowsiness or lethargy, but severe medical outcomes (ICU admission, death) were significantly more prevalent in the US (odds ratio 18.82, 95% CI = 5.85-60.56).

The French Addictovigilance system received 20 reports of kratom-associated cases from 2007-2020 (14 since 2016) (Le Boisselier et al., 2021). The major manifestations were dependence and withdrawal, anorexia, and psychosis. There was one death (2018) and one case of severe hepatitis (Le Boisselier et al., 2021).

Chronic kratom use has been associated with at least 92 cases of liver toxicity (Ballotin et al., 2021; Schimmel & Dart, 2020). Common presenting signs and symptoms include abdominal discomfort, jaundice, pruritus, and dark-colored urine. These typically start about 3 weeks after initiation of kratom use (range 1-8 weeks) and resolve within one month of stopping kratom use. Liver transplantation was reported in only one case, who also had *Salmonella* infection (Schimmel & Dart, 2020). The histologic picture can be hepatocellular, cholestatic, or mixed.

Small cross-sectional studies of kratom users in Southeast Asia find no significant association between long-term, frequent kratom use and clinically significant abnormalities in standard clinical laboratory blood tests, such as complete blood count, blood chemistries, and lipid profiles (Abdullah et al., 2020; La-up, Saengow, & Aramrattana, 2021; Singh et al., 2018a) or blood concentrations of gonadal hormones (Singh et al., 2018b). A 42-year old US man developed hypogonadotropic hypogonadism with elevated prolactin and decreased testosterone blood concentrations, fatigue, and decreased libido while taking kratom (LaBryer et al., 2018). No other causes were identified during medical evaluation, and he returned to normal within two months of stopping kratom use.

There are several published case reports of cardiac arrhythmia or cardiac arrest associated with kratom use in Southeast Asia but all cases likely involved other substance use and none measured mitragynine concentrations (Abdullah and Singh, 2021a). A cross-sectional study of 100 regular kratom users (estimated average mitragynine intake 7.06 mg/kg/day) in Malaysia found no significant differences in electrocardiographic abnormalities compared with 100 non-kratom-using control subjects (Abdullah et al., 2021). The kratom users were significantly more likely to have sinus tachycardia (odds ratio 8.61, 95% CI 1.06-70.17). A study of a convenience sample of 9 adult (18-43 years old) Malaysian men who were chronic (2-14 years), daily kratom users (2-6 glasses/day of “brewed kratom juice”) administered an ECG, transthoracic echocardiogram, and peripheral blood collection for mitragynine assay within 2-3 hours of their last kratom ingestion (Abdullah and Singh, 2021b). Four respondents had a prolonged QTc interval, associated with a significantly higher serum mitragynine concentration (mean [standard deviation] 15.9 [6.4] mg/L) than the 5 respondents with normal QTc interval {5.9 [2.7] mg/L}. There were no other ECG abnormalities. All echocardiograms were normal, except for one respondent with left ventricular hypertrophy and one with “trivial” tricuspid regurgitation. All respondents were daily cigarette smokers (≤ 20 /day); none used alcohol or other drugs. No respondent had a personal or family history of cardiovascular disease.

A cross-sectional survey of a convenience sample of 150 Malaysian men (92% employed, 91% with at least secondary education) who used kratom (59% at least 6 years, 55% more than three times a day) found 4% reported current positive psychotic symptoms (Abdullah et al., 2019). None of the men reported a history of psychiatric disorder; none had used illicit psychoactive substances within the past year (two-thirds had never used).

7. Dependence Potential

A. *Animal Studies*

Repeated oral dosing of rats with mitragynine (15 mg/kg i.p. twice daily for 14 days) (Harun et al., 2020) or of mice with mitragynine (15 mg/kg i.p. daily for 5 days) (Wilson et al., 2021), with kratom alkaloid extract (escalating doses of 30-125 mg/kg [equivalent to mitragynine 14.7-60.7 mg/kg] twice daily for 4 days) (Wilson et al., 2021), or with lyophilized kratom tea (escalating doses of 30-125 mg/kg [equivalent to mitragynine 0.21-0.93 mg/kg] twice daily for 4 days) (Wilson et al., 2020) produced physical dependence, as evidenced by naloxone-precipitated withdrawal signs. These withdrawal signs were substantially less

intense than those precipitated by comparable dosing with morphine. Repeated oral dosing of rats with mitragynine (15 mg/kg i.p. twice daily for 14 days) did not induce spontaneous withdrawal after dosing was stopped (Harun et al., 2020).

B. Human Studies

One clinical trial used the Clinical Opioid Withdrawal Scale (COWS, a standardized, validated rating instrument) to evaluate opioid withdrawal signs and symptoms in 26 Malaysian young men who used oral kratom several times daily for at least 3 years (Vickasingam et al., 2020). COWS scores after overnight abstinence from kratom use or within 24 hours of taking a dose of kratom concoction (containing 1.6 mg/kg mitragynine) were all 0.5 or lower, indicating no opioid-like withdrawal after a period of 10-20 hours of abstinence. This assessment period may have been too brief to allow kratom withdrawal to develop, given that self-reported withdrawal may take up to 48 hours to develop (Grundmann, 2017) and the human elimination half-life of mitragynine is 23 hours (albeit based on one study) (Trakulsrichai et al., 2015).

In-person interviews with convenience samples of long-term daily oral kratom users in Southeast Asia find up to three-quarters reporting withdrawal symptoms after cessation of use (Saingam et al., 2016; Singh et al., 2014; Singh et al., 2018c; Singh et al., 2018d; Suwanlert, 1975). Typical withdrawal symptoms include irritability, anxiety, depression, sleep disturbance, lacrimation, rhinorrhea, muscle and bone pain, muscle spasm, diarrhea, and decreased appetite. The likelihood and severity of withdrawal are positively associated with duration, frequency, and intensity of kratom use.

Cases of kratom withdrawal come to medical attention in the United States literature, but the overall prevalence of kratom withdrawal is unknown (Stanciu et al., 2019). In an online cross-sectional survey of a convenience sample of 8049 US kratom users, 43% reported experiencing uncomfortable symptoms within 48 hours of stopping kratom use (Grundmann, 2017). Kratom withdrawal symptoms reported in the US are similar to those reported in Southeast Asian patients (Stanciu et al., 2019). Withdrawal appears more common among long-term, heavy, daily users. Five cases of opioid-like neonatal abstinence syndrome (e.g., jitteriness, irritability, emesis, feeding intolerance) have been reported in neonates born to mothers who were heavy regular kratom users (up to 16-18 g thrice daily) but not using opioids (Wright et al., 2021). All neonates responded to standard treatment for neonatal opioid abstinence syndrome, i.e., tapering doses of opioids. In some cases, the mother also experienced opioid-like withdrawal in the hospital.

In a 2017 cross-sectional, anonymous online survey of a convenience sample of 2,798 self-selected US adult kratom users, 9.5% reported experiencing kratom withdrawal symptoms (Garcia-Romeu et al., 2020). Their mean (SD) score on the Subjective Opiate Withdrawal Scale (a standardized, validated rating instrument) was 8.8 (8.4), indicating mild withdrawal symptoms.

8. Abuse Potential

A. *Animal Studies*

Kratom extract or mitragynine show rewarding properties in only one of three widely used rat models of abuse potential. Mitragynine (10-90 mg/kg i.p) generates a conditioned place preference (Japarin et al., 2021; Meepong et al., 2019; Sufka et al., 2012; Yusoff et al., 2014; Yusoff et al., 2017; Yusoff et al., 2018), considered a sign of rewarding action. This effect is blocked by the mu-opioid receptor antagonist naloxone, suggesting that it is mediated by activation of the mu-opioid receptor (Yusoff et al., 2017). However, a methanolic extract of kratom leaves (50-300 mg/kg i.p.) does not generate conditioned place preference (Sufka et al., 2012), nor does lyophilized kratom tea (100 mg [equivalent to 0.74 mg mitragynine]/kg, 1 g [7.4 mg mitragynine]/kg orally) in mice (Wilson et al., 2020). In contrast, mitragynine is not self-administered by rats (25-150 µg or 0.1-3.0 mg iv) (Hemby et al., 2108; Yue et al., 2018) and does not alter the reward threshold (lowering threshold is rewarding) or response latency for intracranial self-stimulation (ICSS) at 1-30 mg/kg ip or intragastric (Behnood-Rod et al., 2020) (Dr. Patrick Beardsley, personal communication). Mitragynine increased the reward threshold at the highest dose studied (56 mg/kg ip), suggesting an aversive action (Behnood-Rod et al., 2020).

7-Hydroxymitragynine (5, 10 i.v.) is self-administered by rats (Hemby et al., 2018). This effect is blocked by the selective mu-opioid receptor antagonist naloxonazine and the selective delta-opioid antagonist naltrindole, suggesting dual mu- and delta-opioid receptor mechanisms. 7-Hydroxymitragynine had inconsistent effects on ICSS reward threshold in two studies. In one study, lower doses (0.1-1.0 mg/kg i.p. had no effect, while a higher dose (3.2 mg/kg i.p.) increased ICSS reward threshold (with no change in response latency), suggesting an aversive action of high-dose 7-hydroxymitragynine (Behnood-Rod et al., 2020).. In another (unpublished) study, 7-OH-mitragynine (0.3-3 mg/kg ip) lowered the ICSS threshold (Dr. Patrick Beardsley, personal communication). We are not aware of any studies of 7-hydroxymitragynine and conditioned place preference.

Rats can be trained to distinguish mitragynine (15 mg/kg i.p.) or 7-hydroxymitragynine injections from saline injections, suggesting that these two alkaloids produce distinctive substance-induced internal sensations (Harun et al., 2015; Obeng et al., 2021). Rats do not readily distinguish these two alkaloids from morphine, suggesting that the internal sensations are morphine-like. Rats also do not distinguish mitragynine (10 mg/kg ip) from methamphetamine (1 mg/kg i.p.) (Meepong et al., 2019). 7-Hydroxymitragynine is perceived as more morphine-like than is mitragynine (Obeng et al., 2021).

Kratom methanolic extract (100 mg/kg p.o., 4.4% mitragynine by weight) did not acutely increase dopamine concentration in mouse brain nucleus accumbens, while a reinforcing dose of alcohol did (Vijeeppallam et al., 2019). Increasing nucleus accumbens dopamine concentration is an acute effect of almost all substances of abuse, including opioids (Gardner, 2011).

B. Human Studies

A 2018-2019 anonymous online survey of a self-selected convenience sample of 59,714 US adults weighted to be demographically representative of the entire US population identified 490 respondents with at least one use of kratom in the prior 12 months (Schimmel et al. 2020). About 20% of these kratom users were considered at severe or substantial risk of having a kratom use disorder, based on their responses to a standardized screening instrument (Drug Abuse Screening Test).

In a 2017 cross-sectional, anonymous online survey of a convenience sample of 2,798 self-selected US adult kratom users, respondents rated their typical subjective drug experience on a 100-mm visual-analogue scale (Garcia-Romeu et al., 2020). The mean (SD) rating for “drug liking” was 85.7 (23.7) and for “good effects” 86.4 (23.0), but only 12.0 (20.1) for “high” and 25.1 (27.1) for “euphoric.”

Cross-sectional surveys of convenience samples of regular kratom users in Southeast Asia find many respondents report difficulty reducing or stopping their kratom use (Ahmad and Aziz, 2012; Saingam et al., 2013). However, these surveys rarely find psychosocial impairment associated with kratom use (Singh et al., 2015; Singh et al., 2017).

A review of 161 unstructured kratom experience reports spontaneously posted on a web site for psychoactive substance users between 2001 and 2012 found that 30.4% experienced euphoria and 23.6% experienced relaxation (Swogger et al., 2015). The vast majority of respondents (self-selected convenience samples) in Southeast Asia and the United States in cross-sectional surveys of motivation for kratom use report using to self-medicate a physical or psychological condition, cope with a problem, or enhance energy (Bath et al., 2020; Grundmann, 2017; Saref et al., 2019; Singh et al., 2019). Very few respondents report use for “recreational” purposes; most survey questionnaires do not provide a response option for recreational use. Some respondents in Southeast Asia report using kratom to enhance sociability (Saingam et al., 2013).

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

Kratom and its alkaloids have never been licensed for therapeutic use. Several therapeutic applications have been proposed for kratom and its alkaloids based on preclinical data (see section 4.C.a above) and anecdotal reports from kratom users (Bath et al., 2020; Garcia-Romeu et al., 2020; Grundmann, 2017; Saref et al., 2019; Singh et al., 2019). These include analgesia, treatment of opioid and alcohol use disorders and opioid and alcohol withdrawal, and treatment of depression and anxiety.

10. Listing on the WHO Model List of Essential Medicines

Kratom, mitragynine, and 7-hydroxymitragynine are not included in the WHO Model List of Essential Medicines.

11. Marketing Authorizations (as a Medicinal Product)

None.

12. Industrial Use

None.

13. Non-Medical Use, Abuse and Dependence

The actual prevalence of kratom use and misuse are unknown, as kratom was not included until very recently in large, population-based epidemiological surveys. A 2019 cross-sectional survey of a nationally representative probability sample of 56,136 community-dwelling United States residents at least 12 years old (US National Survey on Drug Use and Health) estimated past-year kratom (powder, pill, leaf) use by 0.7% (95% CI 0.6-0.8%) of the US population (Palamar, 2021). Kratom use was significantly more prevalent among 18-49 year-olds, women, and non-Hispanic Whites. Past-year cannabis use (adjusted odds ratio 4.57, 95% CI 3.29-6.35), cocaine use (adjusted odds ratio 1.69, 95% CI 1.06-2.69), and non-medical use of prescription stimulants (adjusted odds ratio 2.10, 95% CI 1.44-3.05) were all significantly associated with kratom use, while opioid use was not. However, prescription opioid use disorder was significantly associated with kratom use (adjusted odds ratio 3.20, 95% CI 1.38-7.41).

A 2018-2019 anonymous online survey of a self-selected convenience sample of 59,714 US adults weighted to be demographically representative of the entire US population found an estimated prevalence of 0.8% (95% CI 0.7-0.9) for past-year kratom use (an estimated 2.0 million adults) and 1.3% (95% CI 1.2-1.4) for lifetime kratom use (an estimated 3.35 million adults) (Schimmel et al., 2020). Kratom users were more likely than non-users to be younger than 45 years and men.

A 2017 cross-sectional, anonymous online survey of a convenience sample of 2,798 self-selected US adult kratom users found that 9.9% met DSM-5 criteria for past-year mild kratom substance use disorder, 1.8% for moderate kratom substance use disorder, and 0.6% for severe kratom substance use disorder (Garcia-Romeu et al., 2020).

A 2016 cross-sectional survey of a stratified random sample of 30,411 Thailand residents (15-64 years old) weighted to be representative of the national population found that 14.3 % (95% CI 13.7-14.9) reported lifetime use of kratom leaves and 14.2% (95% CI 13.6-14.8) use of kratom cocktail (kratom leaf decoction mixed with another beverage); 2.1% (95% CI 1.9-2.3) past-year use of kratom leaves and 0.7% (95% CI 0.6-0.8) of kratom cocktail; and 1.4% (95% CI 1.3-1.5) past-month use of kratom leaves and 0.4% (95% CI 0.3-0.5) of kratom cocktail (Wonguppa and Kanato, 2018).

There are little data available on the prevalence of treatment for kratom use disorder, in part because kratom was not included on most standard questionnaires until recently. In 2018, Malaysia reported 16 admissions for the treatment of kratom use disorder, out of 26,449 total admissions for substance use disorders (excluding alcohol and tobacco) (United Nations Office on Drugs and Crime, 2020).

In an anonymous online survey of more than 110,000 self-selected psychoactive substance users from more than 25 countries conducted November-December, 2019, 3.5%

of respondents reported using kratom in the prior 12 months (Global Drug Survey, 2020). Kratom ranked 21st in prevalence among all psychoactive substances mentioned.

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

More than 300 deaths associated with kratom have been reported in the peer-reviewed medical literature through 2019 (Corkery et al., 2019; Eggleston et al., 2019; Mata and Anders, 2020; Olsen et al., 2019). The vast majority of cases were in the US and Western Europe and occurred since 2015. 127 kratom-associated deaths were reported to the UNODC Early Warning Advisory Tox-Portal between January 2017 and December 2020: 63.8% from the US (the majority from California), 30.7% from Thailand, 3.1% from Sweden, 1.6% from Australia, and 0.8% from Finland (UNODC Early Warning Advisory Tox-Portal, 2021). More than four-fifths of cases (84%) were in men; almost one-third (30.7%) were 16-24 years old, almost one-half (48%) were 25-44 years old, one-fifth (19.3%) were 45-64 years old, and 2% were older than 64 years old. The causal role of kratom was not provided in 40% of cases. Among the remaining cases, a causal relationship with kratom was considered a “high” likelihood in 20%, a “medium” likelihood in 62.3%, and present but not contributory in 17.6%. In the high likelihood cases, mitragynine concentrations ranged from 118-3390 ng/mL in peripheral blood, 320 ng/mL in femoral blood, 39-543 ng/mL in heart blood, and 480 ng/mL in blood from a body cavity. A study of 35 deaths in Northern Nevada, US between 2015-2020 in which mitragynine was detected in blood post-mortem found no significant difference in mitragynine blood concentration between the 27 cases in which kratom was considered as contributing to death (mean [standard deviation] 269.4 [392.5] ng/mL, range 8.7-1800 ng/mL) and the 8 cases with other causes of death (315 [297.2] ng/mL, range 110-980 ng/mL (Schmitt et al., 2021) For comparison, in two small studies of controlled administration of kratom extracts to adult Southeast Asian men who were experienced kratom users, oral mitragynine administration of 20-23 mg (as kratom tea) or 1.6 mg/kg (as kratom decoction) produced maximum peripheral blood concentrations of 50-100 ng/mL (Trakulsrichai et al., 2015) or 829-5034 ng/mL (Vicknasingam et al., 2020; Dr. Marek Chawarski, personal communication), respectively This lack of association between mitragynine blood concentration and risk of lethality suggests that kratom consumption was not a causal factor in the vast majority of kratom-associated deaths, but rather was an incidental finding.

A 2019 review of 156 kratom-associated deaths identified by published literature and internet searches and UK mortality registries found that the majority were White (100%), young adult (mean age 32.3 years) men (80%) with a history of substance abuse (95%) (Corkery et al., 2019). The 152 kratom-associated overdose deaths reported to the US State Unintentional Drug Overdose Reporting System (SUDORS) in 27 states from July 2016 through December 2017 chiefly involved primarily White (91.5%) men (76.3%) with a history of substance misuse (80.9%) (Olsen et al., 2019)

In a series of 11 unintended drug overdose fatalities in Sweden associated with krypton (combination of kratom and the opioid analgesic O-desmethyltramadol), the mitragynine blood concentrations were 20-180 ng/mg, suggesting possible additive mu-opioid receptor action (Kronstrand et al., 2011).

Attributing causality to kratom in a kratom-associated death can be difficult for several reasons (Papsun et al., 2019). First identification of the two major active compounds, mitragynine and 7-hydroxymitragynine can be problematic due to their instability over long periods at room or body temperature and the need for highly specific assays to distinguish them from their stereoisomers. Second, many cases do not receive comprehensive toxicological evaluation and some novel psychoactive substances (NPS) will remain undetected because accurate assays are not yet available. Third, most cases involve multiple substances, rather than only a kratom alkaloid. A review of 156 published and otherwise identified cases found that one or more other drugs were present in 95.6% of the cases for which toxicology was available (Corkery et al., 2019). The commonest other drugs were opioids, stimulants, and sedatives. Mitragynine/7-hydroxymitragynine was considered as contributing to the cause of death in 23% of cases, including the 6 cases in which no other substances were identified. The mean (range) mitragynine blood concentration was 398 (3.5-890) ng/mL in cases with no other substances present and 890 (0.9-16,000) ng/mL with other substances present. Among the 152 cases reported to the US SUDORS, other drugs were present in 92% of cases, including fentanyl/fentanyl analogues (65.1%), heroin (32.9%), benzodiazepines (22.4%), prescription opioids (19.7%), cocaine (18.4%), alcohol (12.5%), and methamphetamine (8.6%) (Olsen et al., 2019).

In a series of 15 kratom-associated deaths in Colorado, USA from 1999-2017, none were considered clearly due to kratom, after a comprehensive forensic analysis including toxicology (Gershman et al., 2019). In a series of 20 kratom-associated deaths evaluated in Orange County, California US in 2017 and 2018, three cases were considered due to mitragynine (no other drugs found), in 13 cases mitragynine was considered contributory (other drugs found), and in four cases mitragynine played no role (Mata and Anders, 2019), Mitragynine blood concentrations were 1590–3420 ng/mL in the first group and 24.6–1210 ng/mL in the second group. In a series of 35 kratom-associated deaths evaluated in Northern Nevada US in 2015-2020, 8 cases were considered definitely not caused by substance toxicity (e.g., death attributed to gunshot wound, cardiac disease) (Schmitt et al., 2021). The 27 cases considered due to substance toxicity all had substances other than mitragynine identified (opioids 81.5%, benzodiazepines 33.3%, ethanol 33.3%, amphetamines 25.9%, nitrous oxide 7.4%, aripiprazole 3.7%). In the case where aripiprazole was the only other substance identified, phenibut was found at the scene but not tested for. In a convenience sample of 583 post-mortem blood samples sent by US medical examiners to a national forensic reference laboratory between October 2016 and December 2018, the mean (standard deviation) mitragynine concentration was 372 (574) ng/mL, median 140 ng/mL, and range 5.9-4,400 ng/mL (Papsun et al., 2019). For comparison, mitragynine peak blood concentrations were 18.5-105 ng/mL in 10 Thai kratom users taking 6-10 mg mitragynine daily (Trakulsrichai et al., 2015).

Kratom was associated with 90 driving under the influence of drugs (DUID) reports between January 2017 and December 2020—all from the US (UNODC Early Warning Advisory Tox-Portal, 2021). About four-fifths (82%) involved men. However, a direct causal link with kratom could not be established in the majority of cases. In the US state of North Carolina, mitragynine was identified in only six DUID cases between 2014 and 2017 (Papsun et al., 2019). In 2018, mitragynine was identified in 20 cases (out of about 17,500

submissions)—mean (SD) blood concentration 106 (117) ng/mL, median 75 ng/mL, range 11-490 ng/mL. Urine drug testing of 1635 consecutive motor vehicle drivers approached at 13 sites in Thailand between December 2005 and May 2006 identified 0.9% as kratom users (i.e., mitragynine detected in their urine) (Ingsathit et al., 2009). The most frequently detected substances were alcohol (5.5%), antihistamines (2.0%), amphetamine (1.8%), and cannabis (1.1%).

The number of blood samples received for mitragynine testing by a prominent US national forensic reference laboratory (chiefly post-mortem and DUID cases) increased from less than ten per month from October 2012 through January 2016 to 11-40 per month through July 2017 to 41-80 per month through December 2018 (Papsun et al., 2019). The number of samples testing positive for mitragynine increased from two in 2012 to 785 in 2018.

15. Licit Production, Consumption and International Trade

Cultivation of *Mitragyna speciosa* is legal in Southeast Asia. According to an unverified report, Indonesia has a large export trade of kratom leaves to Western countries (Wikipedia, 2021).

16. Illicit Manufacture and Traffic and Related Information

More than 99% of global seizures of kratom over the past decade have been in Southeast Asia (United Nations Office on Drugs and Crime, 2021). Seizures have increased over the past 5 years from about 57 tons in 2015, 400 tons in 2016, 285 tons in 2017, 170 tons in 2018, and 398 tons in 2019.

17. Current International Controls and Their Impact

Kratom, mitragynine, and 7-hydroxymitragynine are not currently under international control under UN treaties. The Association of South East Asian Nations (ASEAN) banned kratom from inclusion in traditional medicine or health supplements in 2013 on the grounds of being “harmful to human health” (Association of South East Asian Nations, 2013). Thailand made kratom a legal herb on 23 August 2021 (Laohong, K-o, 2021).

18. Current and Past National Controls

Kratom, mitragynine, and 7-hydroxymitragynine were under no national controls until about 15 years ago. Since then, they are banned or regulated as controlled psychoactive substances or herbal supplements in several dozen countries globally. At the national (federal) level in the United States, kratom cannot be marketed as a dietary supplement and is considered a drug of concern by the Drug Enforcement Administration (DEA). Kratom is banned in 6 US states and several cities. Canada bans the marketing of kratom for human consumption (United Nations Office on Drugs and Crime, 2021).

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

None

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 44th ECDD: evaluation of kratom, mitragynine, 7-hydroxymitragynine

Data were obtained from 98 Member States (12 African Region, 12 Eastern Mediterranean Region, 37 European Region, 14 Region of the Americas, 7 South-East Asia Region and 16 Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire was 9 (1 African Region, 2 Eastern Mediterranean Region, 2 European Region, 2 Region of the Americas, 1 South-East Asia Region and 1 Western Pacific Region), leaving 89 countries that agreed to provide data.

Of the 89 countries who agreed to provide data, 35 countries had information on kratom, mitragynine, 7-hydroxymitragynine (Table 1).

Table 1. Numbers of countries providing information on kratom, mitragynine, 7-hydroxymitragynine

Region	Number of countries without information	Number of countries with information on substance
African	5	0
Eastern Mediterranean	6	0
European	10	21
Region of the Americas	7	5
South-East Asia	2	2
Western Pacific	5	7
Total (70)	35	35

APPROVED MEDICAL, SCIENTIFIC OR INDUSTRIAL USE

No countries reported approved human medical products and veterinary products containing Kratom, mitragynine, 7-hydroxymitragynine.

Medical use

One country (South East Asia) described kratom, mitragynine, 7-hydroxymitragynine as being used as a part of traditional medicine.

Scientific use

Three countries (2 Region of the Americas, 1 Western Pacific) reported kratom, mitragynine, 7-hydroxymitragynine was being currently used in medical or scientific research (excluding use as an analytical standard) in their country (such as in clinical trials for any human or veterinary indication). One country (Region of the Americas) stated that there was government sponsored research on the “basic pharmacology and potential therapeutic value of mitragynine for disorders, including opioid withdrawal syndrome”. Another country (Region of the Americas) described a “phase I trial to evaluate the safety of different Kratom related formulations in healthy adult participants”. One country (Western Pacific Region) stated there was “scientific research” being

conducted, with no further details provided.

Industrial use

One country (Region of the Americas) described kratom, mitragynine, 7-hydroxymitragynine was being used for industrial or other non-medical/non-scientific purposes in their country – more specifically, for industrial purposes related to rubber.

EPIDEMIOLOGY OF NON-MEDICAL USE

Eighteen countries (12 European, 3 Region of the Americas, 1 South East Asia, 2 Western Pacific) reported there is evidence of the use of kratom, mitragynine, 7-hydroxymitragynine for non-medical use in their country (use outside of the medical, industrial or scientific context).

Routes of administration and formulations

The most common route of administration for kratom, mitragynine, 7-hydroxymitragynine reported was oral and smoking (Table 2).

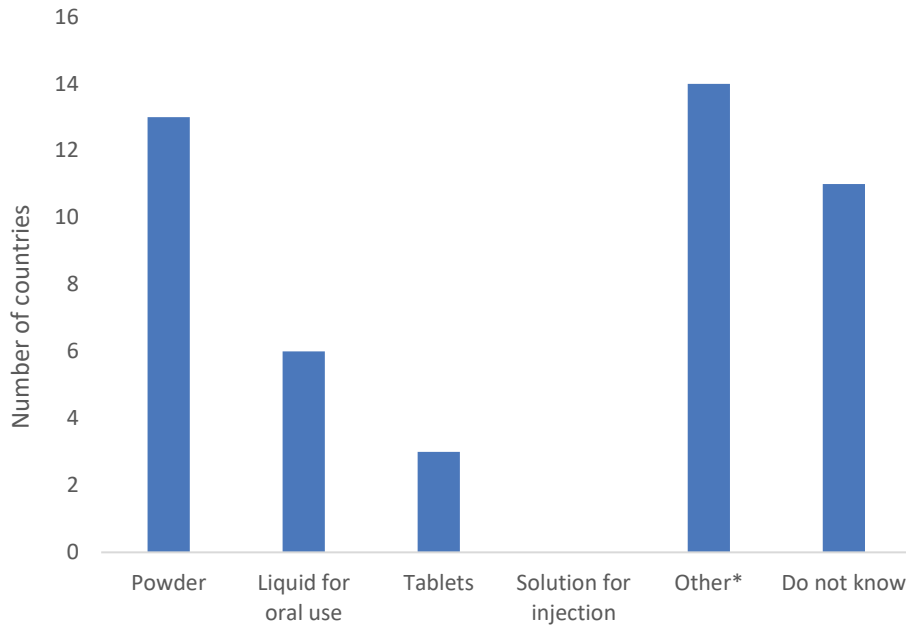
Table 2. Reported routes of Kratom administration

Route of administration	Number of countries
Oral	14
Smoking	5
Inhalation	1
Sniffing	1
Injection	0
Other*	3
Do not know	13

*Other routes of administration included tea/hot-water extraction (n=3 countries) and chewing (n=1; same country that specified tea).

The most commonly reported formulations of kratom, mitragynine, 7-hydroxymitragynine were powder, herbal mixture and liquid for oral administration (Figure 1). One country (European Region) provided the specific description that “the seizures have been herbal material as raw or fine powder e.g. for infusion and capsules containing the powdered herbal material for oral use”.

Figure 1. Formulations of kratom, mitragynine, 7-hydroxymitragynine

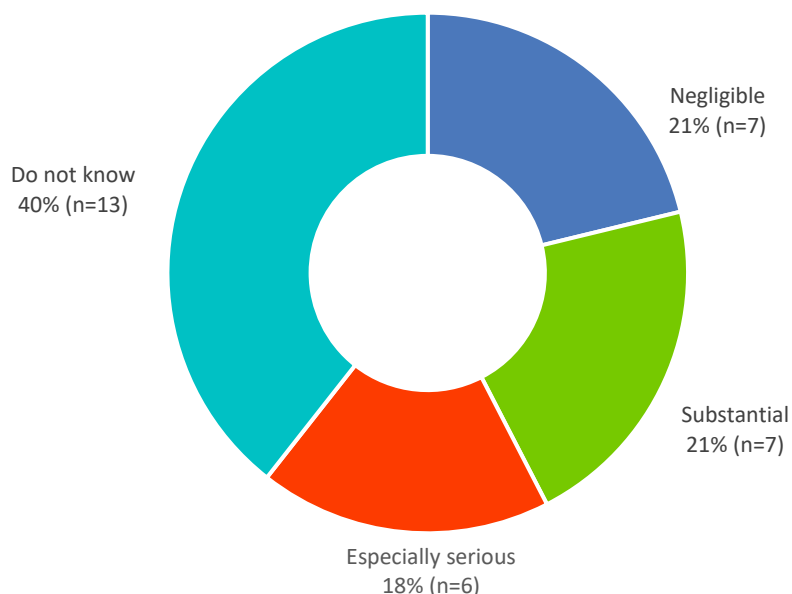


*14 countries noted other formulations, mainly describing herbal mixtures (n=13), and capsule packaging (n=5).

Perceived negative health impact

Thirteen countries (6 European, 3 Region of the Americas, 1 South East Asia, 3 Western Pacific) reported the level of negative health impact due to kratom, mitragynine, 7-hydroxymitragyninenon-medical consumption as “especially serious” or “substantial” (Figure 2).

Figure 2. Countries reporting negative health impact of the non-medical consumption of kratom, mitragynine, 7-hydroxymitragynine.



A country (Region of the Americas) noted “Mitragynine has been encountered on the illicit drug market and has been positively identified in 583 postmortem cases”. Another country from the same region noted “There has been at least one death believed to be caused by Kratom intoxication”. A second country in the Region on the Americas reported from their adverse reaction database three reports involving kratom reported from a hospital which included events (one of each) including acute hepatic failure, acute kidney injury, cholecystitis, cholelithiasis, dizziness, gastroesophageal reflux disease, increased hepatic enzymes, hepatitis, malaise, mental disorder, mental impairment, nausea, rhabdomyolysis and positive salmonella test.

One country (European region) responded there had been kratom, mitragynine, 7-hydroxymitragynine “Seizures and findings in femoral blood in cases of deaths, poison information centre calls”.

A country (Western Pacific) which noted “substantial” negative health impact of kratom, mitragynine, 7-hydroxymitragynine in their country further remarked that “traditionally it may have been consumed for some health benefits. Based on a study on kratom users conducted by [a university in our country] kratom consumption was found to not cause impairment in quality of life of kratom users except for severe kratom dependence which may cause deterioration in physical well-being of users. Nevertheless, we have also seen reports by [our Police force] regarding seizures of concoctions of kratom mixed with other substances (i.e. Coke, cough syrup) for consumption, indicating some form of substance abuse. In addition to the fact that consumption of kratom can cause dependence, this is a significant cause for concern to public health.”

Emergency Department visits

Six countries (3 European, 2 Region of the Americas, 1 South East Asian) were aware of emergency room/department (ED) visits related to kratom, mitragynine, 7-hydroxymitragynine. Five of these

countries (2 European, 2 Region of the Americas, 1 South East Asian) were able to provide further remarks on these ED/hospital visits.

One country (South East Asia) described ED patients as presenting with “running nose, watery eyes, insomnia”. One country (Region of the Americas) reported data from a national poison control data system where “there have been incidence of agitation, tachycardia, drowsiness, seizure, respiratory depression, and coma”.

One country (European) noted “Since 2007, at least 30 patients have presented symptoms after consumption of kratom, mitragynine, 7-hydroxymitragynine alone or in association with other substances. Use disorder, dependency, withdrawal syndrome, anorexia/weight loss, psychiatric decompensation, toxic hepatitis. Nausea, abdominal pains, respiratory depression”. Another country (European) noted that Kratom was consumed with other substances in all the ED presentations which presented with “Reduced consciousness, tachycardia, hypertension, agitation, hallucination, paranoid ideation, hyponatraemia, ALT/AST increased, CK increased, hypothermia, abnormal sweating, vomiting, seizure, mydriasis, epilepsy, bradycardia, depression”.

Deaths

Two countries (1 European, 1 Region of the Americas) reported one death each where kratom, mitragynine, 7-hydroxymitragynine was the only substance involved, one death occurring in 2018 and one in 2020.

Six countries (4 European, 2 Region of the Americas) reported a total of 590 fatalities where kratom, mitragynine, 7-hydroxymitragynine and other substances were involved in the death (years 2013-2020). Of note is that one country (Region of the Americas) reported the bulk of these deaths - 583 deaths where Kratom and other substances were involved over the years 2013-2018.

One country (European) reported a kratom, mitragynine, 7-hydroxymitragynine related death in 2020 where it was unknown whether other substances were involved.

Drug Dependence

Four countries (2 European, 1 South East Asian, 1 Region of the Americas) reported they were aware of people presenting to drug dependence treatment in their country due to use of kratom, mitragynine, 7-hydroxymitragynine.

CURRENT DRUG CONTROL

Eighteen countries (14 European, 4 Western Pacific) responded kratom, mitragynine, 7-hydroxymitragynine is currently controlled under national legislation to regulate its availability.

Another country (Region of the Americas) reported that “Kratom, mitragynine, 7-hydroxymitragynine – mitragynine (or 7-hydroxymitragynine) is a substance that can be extracted from Kratom plant. One country reported that since it is an isomer of Folicodine (listed nominally

under [the List of Narcotic Drugs that can have medical use]), mitragynine is also under the control of [the List of Narcotic Drugs that can have medical use].

Table 3 shows the main reported activities involving kratom, mitragynine, 7-hydroxymitragynine.

Table 3. Reported activities involving kratom, mitragynine, 7-hydroxymitragynine for purposes other than medical, scientific or industrial use.

Activity	Number of countries
Trafficking	9
Smuggling (from other countries)	8
Internet sales (seller or website located in respondent's country)	5
Internet sales (other or location of sellers and website unknown)	5
Internet sales (from abroad to buyers in respondent's country)	4
Production of consumer products containing the substance	2
Direct sales	2
Diversion	1
Do not know	12

Seizures

Eight countries (4 European, 2 Western Pacific, 2 Region of Americas) reported seizures of kratom, mitragynine, 7-hydroxymitragynine in 2021. Seizure numbers ranged from 1 to 2546, and seizure quantities ranged from 4 grams to 156891kg (Table 4).

Thirteen countries (7 European, 4 Western Pacific, 2 Region of Americas) reported seizures of kratom, mitragynine, 7-hydroxymitragynine in 2020. Seizure numbers ranged from 1 to 4970, and seizure quantities ranged from 15 grams to 298120 kg.

Nine countries (5 European, 2 Western Pacific, 2 Region of the Americas) reported seizures of kratom, mitragynine, 7-hydroxymitragynine in 2019. Seizure numbers ranged from 1 to 3882, and seizure quantities ranged from 428 grams to 162945 kg.

Table 4. Reported seizures of kratom

Year	Number of countries reporting seizures	Number of seizures
2021	8	2668
2020	13	5478
2019	9	4485

Thirty two countries (20 European, 6 Western Pacific, 3 Region of the Americas 2 South East Asia, have the forensic laboratory capacity to analyse kratom, mitragynine, 7-hydroxymitragynine.