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REVIEW

# The pharmacology and toxicology of kratom: from traditional herb to drug of abuse

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**Abstract** *Mitragyna speciosa* (Rubiaceae), commonly known as kratom, is a tropical tree with a long history of traditional use in parts of Africa and Southeast Asia. In recent years, kratom has gained popularity for use as a recreational drug across the globe. Relatively new to the illicit market and used in a manner different from its traditional applications, preparations of kratom are touted by many as a safe and legal psychoactive product that improves mood, relieves pain, and may provide benefits in opiate addiction. Available literature was reviewed for *M. speciosa* via PubMed, Google Scholar, CINAHL, and EBSCO to summarize its traditional uses, phytochemical composition, pharmacology and toxicology of proposed active constituents, and potential for misuse and abuse. Research has demonstrated that both stimulant and sedative dose-dependent effects do exist, but a growing concern for the drug's effects and safety of use has resulted in national and international attention primarily due to an increase in hospital visits and deaths in several countries that are said to have been caused by extracts of the plant. The main active alkaloid substances in kratom, mitragynine and 7-hydroxymitragynine, present with a range of CNS stimulant and depressant effects mediated primarily through monoaminergic and opioid receptors. Recently, Palm Beach County, located in the southeastern corridor of Florida, has considered regulating kratom due to public safety concerns following the death of a young adult. At the local, state, and even federal levels, governments are now being confronted with the task of determining the safety and the possible regulation of kratom extracts. There are currently no standard analytical screening techniques for mitragynine and its metabolites following ingestion limiting its detection to more sophisticated techniques like liquid chromatography-mass spectrometry to determine kratom use. The growing concern of the abuse potential of kratom requires careful evaluation of its benefits and potential toxicities.

**Keywords** Kratom · Stimulant · *Mitragyna speciosa* · Psychoactive · Drug abuse

## Introduction

At a time where new synthetic drugs such as cannabinoids and bath salts are increasingly observed in both the clinical and medicolegal setting [1–3], the natural products of *Mitragyna speciosa*, otherwise known as kratom, have also seen increased reports of misuse and abuse. Since the regulation of numerous spice and bath salt compounds, attention has seemingly shifted toward this "new" drug. Historically, kratom has been used by civilizations for many centuries. Cultures located in areas of Southeast Asia have been cultivating and using kratom for several thousand years [4, 5].

Although not new, the drug is, however, novel to the majority of the USA, Europe, and South America and its popularity is on the rise [6]. Its growing misuse and abuse has caused public concern illustrated by recent media attention focusing on its physical effects and implications to society. Moreover, governmental entities are expressing concerns, and local, state, and federal lawmakers are facing challenges in determining the severity of an emerging drug and enacting reasonable regulation.

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This review will provide an overview of the appearance and traditional use of kratom, its current use and prevalence, chemistry and pharmacology of the proposed active ingredients, and analysis of the plant material and biological specimens such as blood and urine, as well as discuss some of the issues that are being experienced in local communities. Finally, discussion of legal concerns and where society is headed concerning regulation will be considered.

## Methods for literature search

All authors evaluated literature via the available databases PubMed, Google Scholar, CINAHL, and EBSCO to gather the current state and development of the composition, ethnopharmacology, analysis, and abuse potential for *M. speciosa*. Search terms used were "*Mitragyna speciosa*" or "kratom" in combination with "pharmacology," "botany," "history," "analysis," "detection," "regulation," and "abuse". Essential literature as well as recent reports of abuse were included in this review.

## Appearance and traditional use

Kratom (*M. speciosa* Korth.) is a tropical tree that is a member of the Rubiaceae or coffee family [4–8]. Dutch botanist Korthals named the genus, *Mitragyna*, due to similarities between the plant's leaves and stigmas compared with a bishop's miter [8]. In Thailand, kratom is sometimes referred as krathom, kakuam, ithang, or thom, while biak-biak or ketum and mambog are street names that respectively descend from Malaysia and the Philippines [6, 8]. The tree is indigenous to tropical and subtropical regions of Southeast Asia including countries such as Thailand, Malaysia, Philippines, Myanmar (Burma), and New Guinea, as well as parts of Africa [4–6]. Growing approximately 15 m tall, the kratom tree possesses relatively large, broad, glossy leaves that are oval shaped and dark green in color (Fig. 1) [4, 5]. The leaves typically grow to lengths of approximately 18 cm and widths of 10 cm [6, 8]. The plant's flowers, nearly 120 florets each, are observed as deep yellow spherical clusters. Wet and humid soil provides optimal growing conditions for kratom. Medium to full sunlight is also ideal. Harvested from the kratom tree, dried leaves and small stems are primarily used for consumption [7].

Historically, kratom was taken to ease opioid withdrawal with use dating back to the 1940s in Thailand [4]. Opium costs soared in 1942 as a result of the Greater East Asia War and drops in opium revenue were experienced. With the increase in cost, users sought out the lower cost kratom to help with withdrawal symptoms. This in turn caused Thai officials to begin controlling kratom in 1943 under the Kratom Act, an effort to gain control in the opium market [4].

Controlled in regions of Southeast Asia, kratom serves as a core component of culture and tradition, particularly in the southern peninsula of Thailand [4, 9]. Similar to that of coca and khat leaves, kratom leaves are traditionally chewed or prepared as a powder. Historically, its stimulant effects have been sought out to help reduce fatigue, in particular for those individuals carrying out manual labor on rubber plantations and seafaring. Known as "chewers," these individuals typically start chewing kratom from the age of about 25 years. Nearly 70 % of "chewers" are males and their day-to-day consumption averages from 10 to 60 leaves. In addition to the workforce, kratom is sometimes used in cultural performances and teashops or as a drink alternative by individuals whom are restricted from alcohol consumption due to their religious beliefs [4].

Dried kratom leaves (Fig. 1) are often crushed and the resulting powder may be inserted into gel capsules or prepared as a hot tea [7]. Plant ashes or baking soda is frequently added to help extract plant alkaloids prior to consumption. One resource states that the addition of lemon juice has also been used to enhance absorption of alkaloids from the small intestines in their ionized form [7] although this is contrary to the common observation that the unionized form of alkaloids is preferred for enhanced absorption. Sugar and honey are sometimes added due to the bitterness of the tea. The powder can also be cooked to yield a syrup-like consistency, which is then compressed into tablets [7].

## Current use and prevalence

Kratom use is no longer limited to traditional and ceremonial uses and its recreational misuse and abuse have been increasing. Gaining popularity over the past several years across Southeast Asia, especially Thailand, is a tea-based cocktail known as 4×100 [4, 7, 8]. Consumed primarily by teenagers and young adults in their thirties, the drink is commonly found to be a concoction of kratom leaves, cough syrup, Coca-Cola, and ice [4]. Yet to gain social acceptance, community discrimination of this cocktail is relatively common, and users are sometimes compared to methamphetamine and heroin addicts. Kratom preparations were among the most commonly abused by high school students at a similar rate to cannabis (2.3–4.9 %) [10].

Public attention from local media and conservative groups have also caused an increase in community discrimination and concern since these cocktails are suspected of containing other drugs such as benzodiazepines and household consumer products including fluorescent tubes, powdered mosquito coils, road paint, and pesticides. Even ashes from the deceased have been added to these cocktails. Such additives are suggested to "enhance" the drink's effects, but there is no scientific

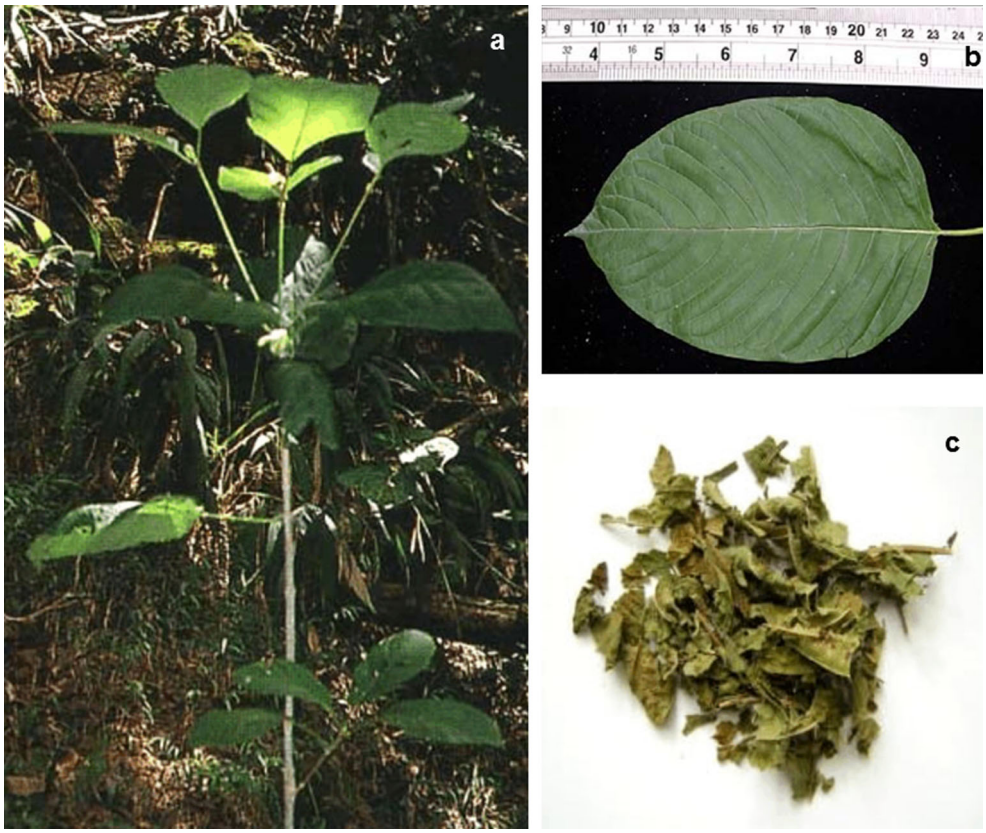


**Fig. 1** Young kratom tree (**a**), fresh kratom leaf to scale (**b**), and dried kratom leaves (**c**). All images obtained from the U.S. Drug Enforcement Administration website [6]

evidence that they actually do so beyond increasing absorption of the alkaloids in their unionized state [4].

Popularity has more recently expanded overseas [6]. As a consequence of opioid addiction, especially in the USA, kratom is frequently marketed for treatment of opioid withdrawal symptoms based on its historical use for this indication in Thailand [3, 6]. A case report described the self-treatment of opioid withdrawal by a patient using kratom in conjunction with modafinil leading to a seizure which resolved after discontinuation of kratom use [11]. In addition to treatment of opioid addiction, kratom is used to help control alcohol withdrawal effects and for control of chronic pain. At variable doses, kratom has also been used to reduce appetite and control stomach cramps and diarrhea, and has been reported to have an important impact on controlling diabetes [4, 12]. Investigations have also reported that kratom extracts show antioxidant and antibacterial activity although this has not been related to traditional or current uses [13]. However, the abuse potential of kratom stems from its cocaine- and morphine-like psychoactive effects which are dose-dependent [6, 7].

Although controlled in regions of Southeast Asia [14], ease of access is not an issue in the USA due to limited legal control of kratom and its active components. Federally and statewide, kratom remains largely uncontrolled and is usually legally available [7].

The prevalence of kratom use in the USA has not been well established to date. Poison centers have reported isolated incidences of kratom use dating back to 2008 [15, 16]. Based on its traditional use and ban in Thailand, the prevalence of kratom has been reported to be in the range of 0.9 % among the general population but reaches up to 59 % of those suffering from a mental disorder or substance use disorder [17, 18].

Purchase remains relatively easy in the USA via head shops, kava bars, and especially the Internet [6, 19]. Marketing and advertising has added to kratom's presence dramatically making it widely accessible both inside and outside the country. In addition, sales of a wide variety of kratom preparations varying from the traditional use of leaves for chewing and brewing, powders, gums, and extracts for users to smoke have become prevalent via Internet distributors [6, 19]. In some instances, kratom has been marketed in similar attractive packaging as many synthetic drugs potentially contributing to its sales success [3].

Adding to kratom's popularity is the fact that it is touted as a legal, psychoactive alternative to other sedative and stimulant-type drugs [20]. As a consequence of its current legal status, kratom preparations are economically obtainable for users compared to opioids and other drugs with an ounce selling for US$10–40 [21].

## Chemistry, pharmacodynamics, and pharmacokinetics

Kratom leaves have been found to contain over 25 alkaloids [4, 7]. The alkaloids mitragynine and 7-hydroxymitragynine (7-HMG) are believed to be the primary active alkaloids in the plant (Fig. 2) [4]. The total alkaloid content in kratom leaves ranges from 0.5 to 1.5 % [7]. Mitragynine makes up approximately 60 % of this extract with 7-HMG accounting for only up to 2 % [21–23]. The alkaloid paynantheine is the second most abundant compound at approximately 10 % of the total alkaloid content (Fig. 2). Other notable analogs are speciociliatine and speciogynine, which comprise about 9 and 7 %, respectively, of the total alkaloid content. The remaining alkaloids (mitraphylline, rhynchophylline, mitralactonal, raubasine, and mitragynaline) each comprise less than 1 % of the total alkaloid content in kratom (Fig. 2).

Mitragynine is an indole-containing alkaloid, structurally similar to yohimbine and voacangine (Fig. 3) [7, 21]. Structural identification occurred in 1965 and its synthesis was achieved 30 years thereafter [7, 9]. Mitragynine is suggested as having approximately 13 times the potency of morphine in regards to its opioid-like effects [3]. It was originally thought that mitragynine was the most active morphine-like chemical component in kratom [7]. Current research suggests that 7-HMG is 4 times more potent in its CNS stimulant and depressant effects than mitragynine [3, 24].

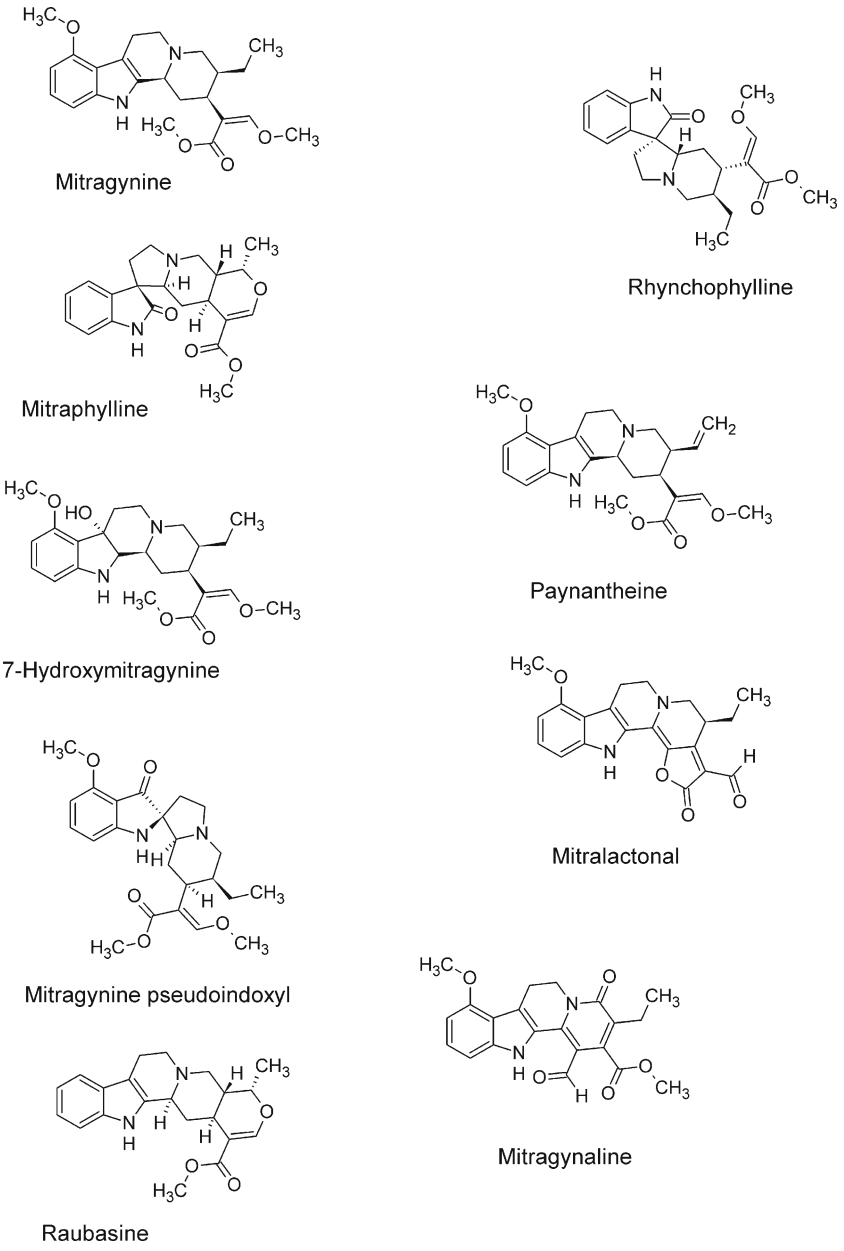


**Fig. 2** Structures of *Mitragyna* compounds

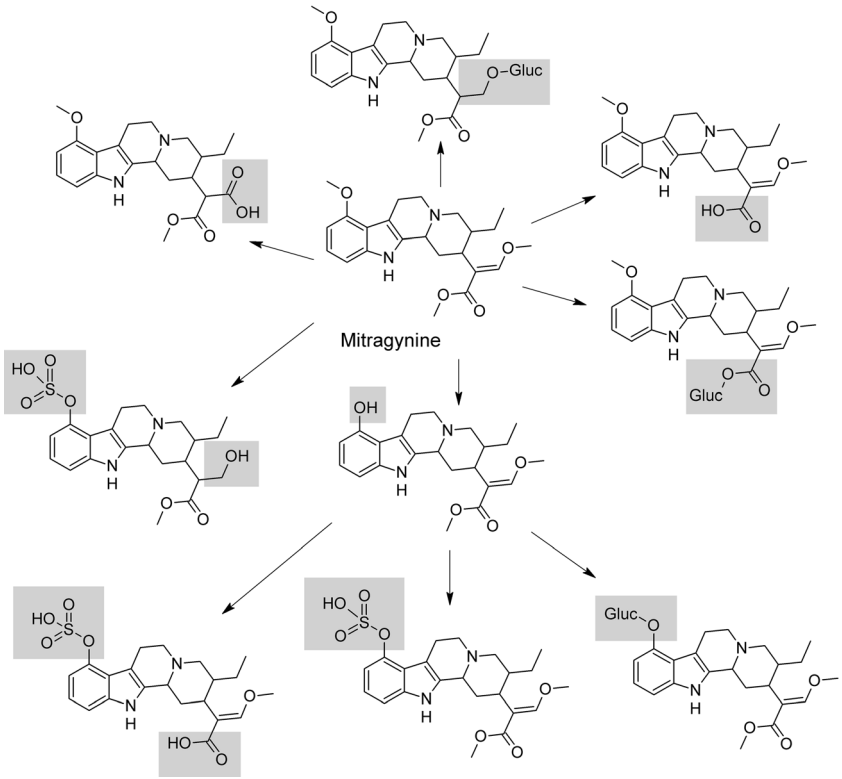


**Fig. 3** Reported metabolites of mitragynine in humans. *Highlighted sections* indicate changes in the molecule through nonenzymatic and enzymatic processes

Kratom effects are complex as it may produce either stimulant or opioid-like effects [7, 21]. Depending on particular needs, the relative levels of stimulation/mood enhancement and sedation/analgesia can be controlled by both the strain of kratom chosen as well as the dosage ingested. With regard to the strain, the red vein variety indigenous to Bali tends to be a more powerful pain reliever, while the white or green vein varieties from Malaysia more often exhibit stimulating and mood-enhancing effects. The white vein tends to provide somewhat more energy than the green vein variety [4, 21]. The relative strength of stimulant and opioid-like sedative effects in each strain is most likely directly related to the varying proportions of different alkaloids present in the leaves of each strain.

Approximately 1–5 g of raw leaves, which is defined as a low to moderate dose, will yield mild stimulant effects (Table 1) [8, 21]. The onset of euphoric effects is experienced in about 10 min after using a few grams of dried leaves [8]. This dosage amount is often related to the stimulant effects commonly used by labor workers to fight fatigue [21]. Not only has increased work capacity been reported by users, but alertness, sociability, and increased sexual desire are said to occur [8]. At this dose, the user may also possess normal to slightly contracted pupils and blushing. Unwanted side effects are generally minimal; however, anxiety and internal agitation have been described [21].

Individuals using from 5 to 15 g of leaves are said to exhibit opioid-type effects (Table 1) [8, 21]. At this dosage, kratom may provide the user with pain and opioid withdrawal symptom relief, with diarrhea being a possible side effect. Both mitragynine and 7-HMG yield analgesic and antinociceptive effects. Euphoria is more often achieved at this higher level, but these effects tend to be less intense as compared with opioid drugs [21].

When exceeding 15 g of kratom leaves, one would expect to experience stupor, mimicking the effects associated with opioids [8, 21]. Initially, sweating, dizziness, nausea, and

**Table 1** Pharmacological effects of kratom

| | Low dose (1–5 g) | High dose (5–15 g) |
|---|---|---|
| Stimulant effects | Increased alertness<br>Physical energy<br>Talkativeness<br>Sociable behavior | Tachycardia |
| Sedative/opioid-like effects | Loss of muscle coordination | Constipation<br>Dizziness<br>Hypotension |
| Adverse effects | Itching<br>Nausea<br>Loss of appetite<br>Increased urination | Dry mouth<br>Sweating |

dysphoria will often result. These effects quickly subside and are followed by calmness and a dreamlike state [8].

Frequent users of kratom have displayed instances of tremor, anorexia, weight loss, seizures, and psychosis [7, 21]. Such individuals are likely using high doses of kratom for a prolonged period of time [7, 21].

Mitragynine and 7-HMG are selective and full agonists of μ-opioid subtype receptors [3, 7, 8, 21]. Mitragynine exhibits activity on supraspinal μ- and δ-opioid receptors causing its characteristic analgesic effects [3, 7, 8, 21]. With consideration to the interactions at the cellular level, studies suggest that neurotransmitter release from the nerve endings at the vas deferens is inhibited [21]. This inhibition is suggested to occur through the obstruction of neuronal calcium ($Ca^{2+}$) channels [7, 22]. Blocked stimulation of serotonergic 5-$HT_{2A}$ receptors and stimulation of postsynaptic alpha-2 adrenergic receptors are thought to contribute to stimulant activity [3, 8]. Additional psychoactivity is said to exist as a consequence of binding affinities exceeding that of morphine at the δ- and κ- opioid central receptors [21]. Moreover, 7-HMG provides high opioid receptor affinity with full agonist properties [8, 21]. While polarity is increased due to the additional hydroxyl group on 7-HMG as compared to mitragynine, increased activity of 7-HMG is otherwise not well understood [21].

Mitragynine is metabolized in humans via phase I and II mechanisms. The parent undergoes hydrolysis at the side-chain methylester in position 16 [7, 8, 21]. *O*-demethylation then takes place at the 9- and 17-methoxy groups. Oxidative and reductive transformations proceed to the intermediate aldehydes, which yield carboxylic acids and alcohols, respectively. A final step involves glucuronide and sulfate conjugate formation as a result of phase II metabolism which is excreted with the urine [7, 8, 21]. In vitro experiments using isolated CYP450 enzymes indicate that kratom extracts inhibit various CYP enzymes, notably CYP 3A4, 2D6, and 1A2. This may lead to clinically significant interactions with other drugs given that a wide range of prescription and OTC medication are substrates for these CYP enzymes [25].

Kratom users can expect to experience full effects in about 30–60 min after ingestion, although onset can be noticeable within about 10–20 min. The half-lives of mitragynine and 7-HMG are about 3.5 and 2.5 h, respectively. Both are eliminated from the body primarily with the urine [21, 26, 27]. The pharmacokinetics following oral administration of mitragynine in humans has been proposed as a two-compartment model based on the observed kinetics in ten healthy human male volunteers [28]. Certain conditions such as prior food consumption or taking kratom in capsule form can delay the initial response. The effects of kratom typically last about 5–7 h, with the strongest effects at about 2–4 h after ingestion, although weak aftereffects can be felt as late as the next day [3, 21, 29, 30]. Current pharmacokinetic data in both animals and humans is limited, and there appear to be a significant variability within each species and differences between species in terms of mitragynine pharmacokinetics (Table 2).

Side effects, particularly for regular heavy users, can include nausea, weight loss, fatigue, constipation, insomnia, dry mouth, frequent urination, and hyperpigmentation of the cheeks [3, 6]. Despite being opiate-like, withdrawal symptoms are generally nonexistent to mild, even for heavy users.

Kratom is considered minimally toxic, but it is important to note that research evaluating its toxic effects on humans is limited, with the vast majority of studies involving animals [7]. The results of such animal studies have been somewhat confusing and contradictory. In one study on dogs in 1972, doses of mitragynine as high as 920 mg/kg produced no evidence of toxicity as measured by tremors and convulsions, while a more recent 2010 study in rats reported that an oral dose of 200 mg of mitragynine had lethal effects [32]. A separate study in rodents reported hypertension and nephro- and hepatotoxicity in higher doses up to 1000 mg [33]. This may point to a species-specific response which remains unexplained as of yet. It is worth mentioning that in order to ingest 200 mg mitragynine, approximately 22–67 g of kratom leaves would theoretically have to be ingested [7, 20–23]. Established dosage amounts are unavailable; however, an individual would have to consume anywhere from 6–10 up to 19–29 spoons full of kratom powder. Careful examination of animal and other studies is therefore warranted [23]. Interestingly, kratom preparations have also been shown to protect against castor oil-induced diarrhea in rats in oral doses of 400 mg/kg comparable to the effect of morphine pointing to at least partial involvement of opioid receptors in its mechanism of action [34].

There are, however, rare documented reports involving kratom toxicity in humans [21, 23]. Seizures and addiction are predominantly experienced by individuals following long-term kratom consumption or an acute overdose. Liver toxicity is also linked to significant kratom overdose [21, 23]. Specifically, intrahepatic cholestasis has been reported [23]. Studies suggest that glutathione-S-transferase is elevated in individuals consuming large doses although this has only been demonstrated in animal studies [23].

The use of kratom in conjunction with other drugs can be problematic [7, 8, 21]. Adverse effects and even death may result. Literature indicates that kratom is sometimes fatally mixed with carisoprodol, modafinil, propylhexedrine, *Datura stramonium*, fentanyl, diphenhydramine, caffeine, morphine, and/or O-desmethyltramadol (“Krypton”) [7, 8, 21, 35].

Some reports indicate that users may become addicted to kratom. However, contradictory data exists concerning the degree of addiction that is experienced due to kratom use [21]. In some instances, it is thought that kratom is less addictive as compared with traditional opioids. In contrast, some

**Table 2** Noncompartmental pharmacokinetic parameters of mitragynine in humans and rats

| Mitragynine<br>All data is mean±standard deviation | | |
|---|---|---|
| Number of data points, species, reference | $N$=10, human, [28] | $N$=6, rat, [31] |
| Terminal half-life ($t_{1/2}$, h) | 23.24±16.07 | 9.43±1.74 |
| Apparent volume of distribution ($V_d$, L/kg) | 38.04±24.32 | 89.50±30.30 |
| Time point of maximum concentration ($t_{max}$, h) | 0.83±0.35 | 1.83±1.25 |
| Clearance (CL, L/h) | 1.40±0.73 | 1.60±0.58 |

case studies suggest kratom addiction to be a significant issue, especially for chronic users [7, 21]. As a consequence, tolerance and cross-tolerance with both CNS stimulant and depressant drugs may result. Withdrawal symptoms consistent with opioids such as morphine are experienced: irritability, dysphoria, nausea, hypertension, insomnia, yawning, rhinorrhea, myalgia, diarrhea, and arthralgias. Agonist and antagonist drugs have been successfully administered to manage withdrawal effects; dihydrocodeine and lofexidine have been found to curb such symptoms in one case report [7, 21, 36].

## Analysis

Mitragynine and 7-HMG are not routinely detected in most drug testing or screening procedures in the clinical and forensic toxicology setting [21]. Since kratom remains licit to purchase and possess in most of the USA and other countries, crime laboratories have not expended resources for purchasing drug standards and validating methods for its analysis [21].

Based on the rise in suspected kratom exposures in recent years, a range of methods have been developed for the analysis of the plant material and other kratom-containing substances including numerous chromatographic techniques, which are most frequently used [37] (Table 3). High-performance liquid chromatography (HPLC), the most common of chromatographic techniques, and other LC techniques coupled with either ultraviolet (UV) or mass spectrometer (MS) detectors (e.g., electrospray) may be used to detect the active alkaloids in kratom leaves [3, 22, 37]. Diode array detection (DAD) is fast and simple but lacks specificity [38]. Linear ion trap, quadrupole, and triple quadrupole mass-specific detection are also suitable for detection of kratom alkaloids.

An objective comparison of chromatographic analyses was performed on a prepared solution containing extracted oxindole and indole alkaloids commonly found in kratom samples, some of which are diastereoisomers to each other. Three techniques were studied: ultra-performance liquid chromatography-mass spectrometry-diode array detection (UHPLC-MS-DAD), supercritical fluid chromatography-diode array detection (SFC-DAD), and gas chromatography-mass spectrometry (GC-MS) (Table 3). Resolution of the alkaloids was accomplished for each of the methods except GC-MS. Separation was limited by diastereoisomers mitragynine and speciociliatine, which is a cause for concern in the effective separation of mitragynine where analysis is conducted by GC. Diastereoisomer separation was not accomplished via GC-MS without derivatization. Both UHPLC and SFC were able to separate the diastereoisomers without the use of a chiral column.

Another study involved purchase of online commercial products suspected of containing kratom [29]. The samples were tested by GC-MS, which is frequently utilized for the

**Table 3** Analytical techniques used in the identification of kratom plants and its constituents

| Analytical technique | Analyte(s) | Matrix | Reference |
|---|---|---|---|
| HPLC-UV/HPLC-DAD | Corynoxine, paynantheine, 3-isopaynantheine, 7-hydroxymitragynine, mitragynine, speciogynine, speciociliatine | Plant | [13, 38] |
| HPLC-MS/UHPLC-MS | Mitragynine, 7-hydroxymitragynine, paynantheine, speciogynine, speciociliatine | Plant, urine, blood | [3, 22, 37, 38] |
| GC-MS | Mitragynine, paynantheine, speciogynine, speciociliatine, corynoxine, 16-carboxymitragynine, 9-O-demethylmitragynine | Plant, urine | [38, 39] |
| icELISA | Mitragynine | Plant | [37] |
| DART-MS | Mitragynine, mitraphylline, paynantheine, 7-hydroxymitragynine, rhynchophylline, epicatechin, ajmalicine, corynoxine | Plant | [40] |
| PCR | rDNA | Plant | [30] |

*HPLC* high-pressure liquid chromatography, *UV* ultraviolet, *DAD* diode array detection, *UHPLC* ultrahigh-pressure liquid chromatography, *MS* mass spectrometry, *GC* gas chromatography, *PCR* polymerase chain reaction, *DART* direct analysis in real time, *icELISA* indirect competitive enzyme-linked immunosorbent assay

analysis and identification of commercial kratom preparations for the presence of active ingredients mitragynine and 7-HMG [3, 22, 29, 39]. The recent study utilized techniques for the identification of kratom that met standards recommended by the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) [29]. Due to kratom preparations yielding nonspecific color reactions, chemical spot tests were not useful in presumptive identification. However, the study determined that thin layer chromatography (TLC) followed by GC-MS was suitable in both screening and confirming mitragynine with limited sample preparation [29].

In addition to chromatographic analyses of kratom plant material and extracts, research exists for the analysis of metabolites found in biological specimens. As an example, LC-MS using a linear ion trap is suitable to identify metabolites of kratom in rat and human urine [3, 22]. High-resolution mass spectrometry (HRMS) with an Orbitrap (OT) analyzer was also successful in detecting the alkaloids in a research setting. Additional LC techniques may detect mitragynine such as UHPLC-MS and LC-MS/MS. In separate experimental procedures, both techniques were performed for the quantitation of mitragynine in rat plasma in order to evaluate pharmacokinetic parameters such as distribution and elimination [3]. Phase I and II metabolites can also be differentiated in human samples [22]. Using rats that were administered certain doses of mitragynine, metabolites of mitragynine, paynantheine, speciogynine, and speciociliatine were all detected by GC-MS [39].

Though less common, there is additional research involving nonchromatographic techniques [38]. Specifically for the analysis of plant-based products, polymerase chain reaction (PCR) and direct analysis in real-time mass spectrometry (DART-MS) were helpful for confirmatory analysis of samples. PCR using restriction fragment length polymorphism (RFLP) was utilized for the analysis of various plant products for the presence of kratom [3, 30]. Kratom could be distinguished from similar and related psychoactive plants. The technique proved useful due to its wide range of application, high accuracy, and ease of use [30]. The latter technique, DART-MS, also has the ability of differentiating between other plants and *Mitragyna* plant varieties [40]. This method provided both rapid analysis and minimal sample preparation [40].

In contrast, rapid preliminary detection of drugs in biological matrices is often desired in forensic toxicology [37]. Immunoassay is frequently used for its sensitivity and ease of use, especially for various drug preparations and biological specimens. For the detection of mitragynine in kratom leaves, indirect competitive enzyme-linked immunosorbent assay (icELISA) was carried out for the detection of mitragynine. This method proved effective as a screening technique for mitragynine in kratom leaves; however, improvements to sensitivity and potentially specificity are desired for applications involving biological fluids [37].

## Present legal situation concerning kratom in the USA

In the past couple of years, kratom use has grown nationally. Internet marketing and retail accessibility have contributed to increased popularity throughout the USA. In fact, kratom's emergence correlates with trends noted in current national drug databases. In one of these drug databases, the System to Retrieve Information from Drug Evidence (STRIDE), drugs seized by DEA forensic laboratories are monitored [6]. The other primary database is the National Forensic Laboratory Information System (NFLIS) which collects analysis data from state and local laboratories. Both databases include data specific to cases of kratom; the data is compiled and quantified concerning mitragynine analysis. Since 2010, cases involving mitragynine have increased. In 2010, only a single instance of mitragynine use was reported. In 2011, there were 44 reports documented. Within only 6 months, this number had increased over 80 % to 81 in 2012 [6]. In 2013 NFLIS reported 181 total cases [32].

The increased use of kratom has contributed to an increase in reports of individuals becoming dependent on kratom [21]. The majority of these instances are case reports involving individuals compulsively using the substance [21]. Emergency room visits have increased with patients becoming ill, especially teenagers using the substance to achieve its euphoric effects [26]. Figures concerning emergency room visits by users of kratom are currently not well documented. Of the data available, there were two instances of emergency visits in 2005 throughout the nation as reported by poison centers. In Phoenix, Arizona, just one of the many metropolitan areas throughout the USA, there were six emergency visits documented in 2011 [26]. Relatively consistent with the observed increase in Arizona, the state of Texas did not have any reported incidents from 1998 to 2008 [15]. From 2009 to 2013, there were 14 incidents of kratom exposure documented by state poison centers [15].

A more recent publication from NMS Labs indicated that 12 % of the postmortem and human performance blood samples submitted for testing from agencies and labs throughout the USA in 2014 contained mitragynine [41]. That is, 55 of the 459 samples contained this component. This is over double the previous year where of the 472 blood samples submitted, 4.7 % or 22 samples were positive for mitragynine [41].

Although death has been attributed to kratom use, there is no solid evidence that kratom was the sole contributor to an individual's death [42]. In most documented instances, mitragynine was detected in combination with other drugs. As an example, death resulted in an individual with high blood concentrations of propylhexedrine and mitragynine—1.7 and 0.39 mg/L, respectively [43]. Propylhexedrine was determined to be the cause of death with mitragynine possibly also contributing to the death. Urine analysis further detected

acetaminophen, morphine, and promethazine [43]. In another event, a fatality was recorded involving multiple drugs, notably mitragynine [27]. Unlike the previous case, a mitragynine blood concentration of 0.60 mg/L was determined. Therapeutic levels of temazepam, diphenhydramine, and dextromethorphan were also detected. Kratom toxicity was declared as the possible cause of death. Interestingly, the autopsy report findings were consistent with opioid toxicity. Pulmonary congestion and edema, as well as urinary bladder distention, were indicated, though nonspecific. Unlike other case studies, the concentration of mitragynine surpassed other drug levels whose effects were determined minimal [27]. A similar fatal report presented with the same postmortem findings of pulmonary edema and urinary retention at a mitragynine peripheral blood concentration of 0.23 mg/L [44]. From these isolated fatalities, it appears that no threshold concentration for lethal mitragynine or kratom exposure can be determined at this point, especially since many cases involve multidrug exposures.

Concerns with kratom in the USA resulting from such case reports caused federal agencies to disseminate information regarding the substance. The DEA Drug and Chemical Evaluation Section published an informational bulletin [6] (Srihari Tella, 2014, personal communication) and listed kratom on its "Drugs and Chemicals of Concern," which include substances monitored by the DEA that are considered to pose a risk to individuals who abuse such substances [45]. However, more reliable research and data is necessary regarding potential health hazards and addictive properties. The drug remains under evaluation and the likelihood of future federal control is currently unknown (Srihari Tella, 2014, personal communication).

The Federal government has taken some steps to reduce its presence in the USA. The DEA officially declared that there is no legitimate medical use for kratom in the USA. As a result, kratom cannot be advertised in this country as a remedy for any medical condition [21]. Early November of 2014, the Food and Drug Administration (FDA) issued an alert due to the increase in the number of shipments of kratom-containing dietary supplements [46]. The FDA concluded that kratom has a limited history of use and insufficient evidence with respect to safety. Therefore, in order to control shipments of the potentially hazardous substance, the FDA may detain products sent from listed vendors without physical examination. Additional vendors may be added to this list based on whether they meet specified criteria [46].

Kratom has followed a slightly different path internationally. United Nation (UN) Member States are not required to follow international drug conventions [4]. Some of these countries are shifting toward the control of kratom and mitragynine due to adverse health effects. *Kratom acetate* and *mitragynine acetate* started coming to light in the early 2000s, a few years ahead of the USA [47]. Surprisingly, mitragynine was not a component of these substances, also known as *krypton*, which contained caffeine and O-desmethyltramadol. It was not until more recently that products referred to as "incense" started containing kratom's active alkaloids. Surveys administered by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2008 and 2001 discovered that kratom ranked near the top of new psychoactive substances most widely offered among khat and *Salvia divinorum*. In 2011, kratom was listed as being the most frequently identified new psychoactive substance for sale in 220 total shops [48].

Thailand initially regulated kratom under the Kratom Act in 1943, which was loosely enforced [4, 49]. The penalty was later reduced by listing the drug as a Schedule 5 substance on the Thai Narcotics Act in 1979. Myanmar (Burma) and Malaysia moved to control kratom in 1993 and 2003, respectively. In 2004, under the Australian National Drugs and Poisons Schedule, Australia listed mitragynine and kratom under Schedule 9. Neighboring New Zealand added kratom and mitragynine under the prescription drug schedule (I) of the Medicines Amendment Regulations Act of 2009 [50]. Meanwhile, six European Union (EU) Member States have moved to control kratom or some of its chemical constituents: Denmark, Latvia, Lithuania, Poland, Romania, and Sweden. South Korea, Israel, and Germany have also enacted controls of either kratom or its alkaloids [50].

On a notably smaller scale, kratom concerns are also being addressed. Several states and cities throughout the USA plan to ban or have banned the substance [51–53]. As was observed with the emergence of bath salts and synthetic cannabinoids, state and local governments have taken interest and action regarding kratom regulation. More precisely, they are faced with whether or not to control the sale and possession of the substance.

In the state of Florida, Sarasota banned the substance in early 2014 [53]. Other Florida counties and even its state legislatures are currently challenged with determining where kratom regulation should stand. Interest has particularly increased in Florida due to the death of a young adult male which was believed to be caused by kratom [54]. The 20-year old plunged to his death after jumping from an overpass [54–56]. His death captured local and statewide attention as the deceased's mother announced and asserted that addiction to kratom contributed to her son's death [54, 57, 58]. The medical examiner's report revealed that kratom was present (not quantitated). Antidepressants citalopram and trazodone, in addition to the analgesic gabapentin, were found at therapeutic levels in the individual's system [54]. As was observed with other case studies, the cause and manner of death could not be contributed to kratom alone.

In Palm Beach County, kratom use appears on the rise as exhibited by the number of medical examiner cases from 2013 to 2014 that contained mitragynine (not quantitated) in blood

samples [43]. In 2013, it was reported that a single deceased individual's blood contained mitragynine. In 2014, there were five cases of positively identified mitragynine. So far this year, two deaths were reported of individuals where mitragynine was identified.

In February 2015, several months since the 20-year-old's death, the Florida Senate introduced a bill in an effort to control kratom or *M. speciosa* as a schedule I substance. The bill was amended to list mitragynine and 7-HMG instead. In April, the proposed senate bill was adopted by the Florida House of Representatives without objection; however, before becoming law, Florida's Office of the Attorney General (AG) must work in collaboration with the Department of Children and Families' Substance Abuse and Mental Health Program Office and the Florida Department of Law Enforcement (FDLE) in order to determine whether the substance fits placement into a controlled substance schedule by December 31, 2015 [53, 59].

It is interesting to note that while some governments are immersed with the idea of whether the substance warrants the need for regulation, some states in the USA are revoking laws originally enacted in order to ban kratom. In the instance of Illinois, mitragynine and 7-HMG were originally Schedule I controlled substances [60]. They were eventually moved to become regulated under the Kratom Control Act which allows legal purchase or possession by those 18 years of age or older [60]. In Arizona, mitragynine and 7-HMG were initially proposed for addition as a controlled substance [61]. The bill was later amended since kratom is not synthetic allowing it to remain legal [61].

## Conclusion

At a time when public awareness is increasing, additional kratom research is necessary. Meanwhile, lawmakers and scientists around the world should continue to monitor kratom use and continue to take efforts focusing on research in order to attain a global view of its current use and abuse potential.

Since the recent death in Florida, counties have considered banning kratom but, as of yet, taken no action [56]. Both Palm Beach and Broward counties have deemed kratom not ready for regulation due to the lack of information demonstrating the substance as being unsafe or hazardous [56]. The position of these counties appears to be consistent with other state and federal legislators throughout the country.

As with any drug of concern, there are many aspects that must be considered in order to help protect society without taking unjustified steps toward regulation whenever there appear to be real advantages. Yet, potential side effects, especially when improperly used, and real health hazards must not go unnoticed. Research of kratom should move forward with close monitoring of any incidents that should arise. As of yet, research has not determined if the medicinal benefits of kratom may prove to outweigh the acute and chronic dangers of its recreational use.

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