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REVIEW

An update on the clinical pharmacology of kratom: uses, abuse potential, and future considerations

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ABSTRACT

Introduction: Kratom (*Mitragyna speciosa*) has generated substantial clinical and scientific interest as a complex natural product. Its predominant alkaloid mitragynine and several stereoisomers have been studied for activity in opioid, adrenergic, and serotonin receptors. While awaiting clinical trial results, the pre-clinical evidence suggests a range of potential therapeutic applications for kratom with careful consideration of potential adverse effects.

Areas covered: The focus of this review is on the pharmacology, pharmacokinetics, and potential drug–drug interactions of kratom and its individual alkaloids. A discussion on the clinical pharmacology and toxicology of kratom is followed by a summary of user surveys and the evolving concepts of tolerance, dependence, and withdrawal associated with kratom use disorder.

Expert opinion: With the increasing use of kratom in clinical practice, clinicians should be aware of the potential benefits and adverse effects associated with kratom. While many patients may benefit from kratom use with few or no reported adverse effects, escalating dose and increased use frequency raise the risk for toxic events in the setting of polysubstance use or development of a use disorder.

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1. Introduction

The tree from which kratom is derived (*Mitragyna speciosa* Korth., Rubiaceae) is native to Southeast Asia and primarily found in Peninsular Malaysia, Thailand, and Indonesia [1]. It is an evergreen tree growing along creeks and in wetland areas. Its leaves have been used for centuries as a treatment for diarrhea, pain, fatigue, and as a substitute for opium when not available [1]. The names kratom, ketum, or biak-biak have also been given to any products derived from the leaves of the tree. In its native countries, fresh kratom leaves are chewed to provide temporary energy or stave off fatigue, while tea infusions are used to relieve pain and diarrhea, improve mood, and reduce opioid and stimulant withdrawal symptoms [2,3].

In Western countries, kratom products primarily consist of dried leaf material that has been processed into herbal teas, powder, tablets, pills, or various extracts [4]. Because many countries do not regulate kratom products, adequate oversight of labeling and content of such products is lacking, resulting in highly variable product quality and composition which may confuse consumers and health-care professionals alike. The prevalence of kratom use varies, with past year and lifetime prevalence ranging from 0.7% to 6.1% in the United States among varying populations, where consumers with a prior substance use disorder presented with a higher prevalence of use compared to the general population [5,6]. Further complicating this estimate is the co-use of kratom with other substances, especially prescription and illicit psychoactive drugs, which may underestimate kratom use through non-reporting.

While kratom may have potential therapeutic applications based on its traditional uses, it is also associated with adverse effects that require careful consideration regarding whether a patient should consume any kratom product. Certainly, health-care professionals should include kratom and other herbals on their list of substances to discuss with patients as part of obtaining a routine medical history.

This review will summarize the current scientific literature on kratom, including its complex pre-clinical and clinical pharmacology, pharmacokinetics and potential drug interactions, toxicology, and abuse potential, and provide a discussion of future considerations of kratom and its proposed active constituents.

2. Chemistry & pre-clinical pharmacology

Mitragyna speciosa leaf material contains many different classes of chemicals including alkaloids, which have been the focus of researchers. Alkaloids garner such attention because

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Article highlights

- Kratom (*Mitragyna speciosa*) is a complex natural product containing more than 40 alkaloids with varying pharmacological properties. The variability in kratom product formulation and composition complicates the clinical presentation in patients using kratom.
- Drug interactions with kratom primarily relate to inhibition of CYP3A4 and CYP2D6 by mitragynine and related alkaloids. This may be of clinical significance given the wide range of drugs that are substrates for these enzymes.
- Kratom user surveys suggest a diverse population with varying motivations for use, including self-treatment of depressive and anxiety disorders, mitigation of substance withdrawal symptoms, and as an analgesic.
- While the putative symptoms related to kratom use disorder appear to be of mild-to-moderate severity, increased dose amount and frequency of use may increase the risk of kratom use disorder, especially in those with prior substance use disorders.

they have historically been identified as pharmacologically active agents, particularly when their effects include changes in behaviors or the perceptions of one's environment. Kratom contains at least 40 different alkaloids [7]. These can be divided into major and minor alkaloids. The most abundant alkaloid is mitragynine, which has been reported to make up 66% of the total alkaloid content [8]. For this reason, researchers have assumed that mitragynine is the alkaloid responsible for the main pharmacological effects of kratom, and the majority of the scientific literature focuses on this compound [9]. However, there are at least four other major alkaloids that occur in the natural leaf material. Taken together, these have been reported to compose approximately 20% of the remaining 34% of total alkaloid content, and combined with mitragynine, they account for 86% of the total alkaloid content [10]. The remaining alkaloids compose the minor alkaloidal content and include over 35 chemicals, accounting for approximately 14% of the total alkaloid content. With one exception, almost no scientific information has been obtained about the pharmacological activity of the minor alkaloids. On the other hand, pharmacological data is accumulating about some of the other major alkaloids, including speciociliatine, speciogynine, paynantheine, and corynantheidine. These four compounds are all chemically related to each other and are structural isomers or diastereomers of mitragynine [11,12]. Chemically, they are classified as corynanthe-type monoterpenoid alkaloids, as they are structurally most similar to other natural products that interact with alpha-adrenergic receptors [13]. They are also secondary metabolites that are thought to be created by the plant to provide it with a survival advantage in its natural environment. The one minor alkaloid that has garnered great attention as possibly being a significant contributor to the pharmacological effects of kratom is 7-hydroxymitragynine. 7-Hydroxymitragynine is an oxidative metabolite of mitragynine resulting from intestinal and liver metabolism in vivo and has demonstrated strong analgesic activity in animal models while also presenting with respiratory depression in higher doses despite its apparent biased G-protein coupled signaling without β-arrestin-2 recruitment [14–16]. Notably, the biased signaling hypothesis leading to less respiratory depression has been called into question, and other mechanisms are likely contributing to the diminished impact of kratom on respiration [17,18]. Many of the other minor alkaloids belong to another chemical class referred to as oxindoles, about which even less is known regarding their pharmacological activity.

In vitro pharmacological screening using a panel of 82 central nervous system drug targets has been conducted for all the major kratom alkaloids [19]. Due to its natural abundance, mitragynine was hypothesized to interact primarily with opioid receptors, and it has been shown to bind most strongly to the μ-opioid receptor ($K_i = 709$ nM) as a partial agonist. In contrast, it is a weak competitive antagonist at κ-opioid ($K_i = 1{,}700$ nM) and δ-opioid ($K_i = 6{,}800$ nM) receptors [20]. Interestingly, mitragynine does not have a high affinity or preference for any one class of receptors and exhibits pharmacological actions through a variety of targets including opioid, serotonin, and adrenergic receptors [12,20]. At serotonin (5-HT) and α-adrenergic receptors, mitragynine binds with affinities in the μM range ($\alpha_{2A} = 2.3$ μM, $\alpha_{2C} = 3.5$ μM, 5-HT_{1A} = 5.9 μM, 5-HT_{2A} = 5.0 μM, 5-HT_{2B} = 1.3 μM) and acts as a partial agonist [12,13,20]. In contrast, other major alkaloids demonstrate greater affinity toward one of these three targets and weaker interactions with the others. Speciociliatine interacts primarily with opioid receptors and has analgesic actions in some animal models but not in others, indicating possible pharmacological differences among species [21,22]. Speciogynine and paynantheine (which only differ by the location of a single carbon–carbon double bond) interact strongly with serotonin receptors, while also interacting moderately with opioid receptors, and to a lesser extent adrenergic receptors [12]. Paynantheine is among the more abundant alkaloids, presenting with mild conditioned place aversion and blocking morphine antinociception at low doses, which may indicate partial antagonist effects at the μ-opioid and partial agonist effects at the δ-opioid receptors [23]. Corynantheidine (which only differs from mitragynine by lacking an -OCH_3 group) binds strongly to alpha-adrenergic receptors and has weaker interactions at opioid ($K_i = 57$ nM at μ-opioid receptor) and serotonin receptors [13,24].

The minor alkaloids mitraciliatine and isopaynantheine induce antinociception in animal models that is primarily mediated through κ-opioid receptor activation and do not appear to cause respiratory depression even at very high doses [24].

3. Pharmacokinetics & drug–drug interactions

In vitro and in vivo pharmacokinetics of kratom alkaloids have been studied both as individually isolated compounds and as complex natural products [11,25]. Higher systemic exposure to kratom alkaloids was observed in one human study when dosed as a kratom tea or as an organic extract than when dosed as individually isolated compounds [25]. Following a single oral dose of kratom (2 g) tea containing mitragynine (eq., 39 mg), speciogynine (eq., 6.4 mg), paynantheine (eq., 11.7 mg), speciociliatine (eq., 10.2 mg), isopaynantheine (eq.,1.0), and mitraciliatine (eq., 1.3 mg) to six healthy volunteers, these alkaloids were quantified in plasma up to 96 h post-dose except for one volunteer who withdrew from

the study 48 h post-dose. The potent but minor metabolite of mitragynine, 7-hydroxymitragynine, was also quantified in plasma samples up to 24 h post-dose. Two major kratom alkaloids, mitragynine and paynantheine, showed fast absorption, and median peak plasma concentrations were observed at 1 h (T_{max}) post-dose. In contrast, mitraciliatine and isopaynantheine showed delayed absorption with median T_{max} of 4.5 h post-dose. Two other kratom alkaloids, speciogynine and speciociliatine, showed median T_{max} of 2 and 2.5 h, respectively. In terms of distribution, mitragynine, speciogynine, and paynantheine (3S) concentration–time data followed a two-compartmental model, whereas mitraciliatine, speciociliatine, and isopaynantheine (3R) exhibited monophasic distribution in humans. All the kratom alkaloids showed high protein binding (>90%) in human plasma, and blood-to-plasma ratios ranged from 0.65 to 1.05. When comparing the dose-normalized systemic exposure of (AUC/Dose) kratom alkaloids after an oral dose of kratom tea, mitraciliatine showed the highest systemic exposure followed by isopaynantheine, speciociliatine, speciogynine, paynantheine, and mitragynine. Mitraciliatine's AUC/Dose was 90.5-fold higher than mitragynine's, with an elimination half-life of 17.8 hr [26]. The major kratom alkaloid mitragynine is primarily metabolized by CYP3A4 with minor contributions by CYP2D6 and CYP2C9 through monooxidation and *O*-demethylation metabolic pathways. Mitragynine carboxylic acid and 9-hydroxycorynantheidine are two major metabolites of mitragynine [14,22,27]. Another pharmacologically active kratom alkaloid, speciociliatine, is also metabolized by CYP3A4 with minor contributions by CYP2D6 to form similar metabolites to mitragynine, including a hydroxylation at position 7 to generate an analogous metabolite like 7-hydroxymitragynine [28]. CYP3A4 is primarily abundant in the intestine and liver, and these organs are responsible for the first-pass metabolism of kratom alkaloids [29]. A small portion of kratom alkaloids is excreted unchanged in the urine, and the fraction of dosed alkaloid excreted unchanged (f_e) was higher for mitraciliatine, speciociliatine, and isopaynantheine (f_e, 0.09–0.1) than for mitragynine, speciogynine, and paynantheine (f_e, 0.003–0.016). 7-Hydroxymitragyine was not present in the kratom product administered to healthy volunteers in one study but it was quantifiable in plasma samples due to the CYP3A4-mediated metabolism of mitragynine. The metabolite-to-parent AUC ratio for 7-hydroxymitragynine formed from the metabolism of mitragynine in humans was 26.5% [26]. Another metabolite resulting from further metabolism of 7-hydroxymitragynine in human plasma is mitragynine pseudoindoxyl, which is a potent μ-opioid receptor agonist (K_i = 0.8 nM) and κ- and δ-opioid receptor antagonist [22,30]. Pre-clinical animal models indicate that there are species-specific differences in terms of bioavailability, metabolism, and pharmacological effects of the alkaloids [28,31].

Kratom alkaloids have been studied for their CYP inhibition potential using human microsomes (liver and intestinal) and recombinant CYP450 enzymes in vitro. Mitragynine and corynantheidine were observed to be potent inhibitors of CYP2D6 with inhibition constants (K_i) of 1.1 and 2.8 μM, respectively [32–34]. Two other kratom alkaloids, speciogynine and paynantheine, have also shown moderate in vitro inhibition of CYP2D6. However, low-dose kratom (2 g) coadministration did not alter the pharmacokinetics of a CYP2D6 substrate, dextromethorphan, in 12 healthy volunteers [33]. CYP3A4, the most common enzyme responsible for xenobiotic metabolism, can be inhibited (midazolam hydroxylase) by corynantheidine, paynantheine, and mitragynine [32]. According to a clinical drug interaction study reported by Tanna et al., the coadministration of a single low dose of kratom tea (2 g, eq to 39 mg of mitragynine) with midazolam led to 1.5- and 1.4-fold increases in the peak plasma concentration (C_{max}) and the area under the plasma-concentration time profile (AUC) of midazolam, respectively, without changing its elimination half-life ($t_{1/2}$). Kratom alkaloid-mediated inhibition of intestinal CYP3A4 could account for the increased C_{max} and AUC of midazolam without changing its $t_{1/2}$ [33]. Based on mitragynine plasma concentration data available from forensic analysis after fatalities [35], it is feasible that coadministration of kratom alkaloids at high doses can lead to significant adverse events due to its interaction with CYP3A4 and CYP2D6, which are responsible for the metabolism of many clinically important drugs [32].

4. Clinical pharmacology

As will be discussed in detail in a subsequent section on 'use pattern surveys,' kratom is likely used by over two million people in any single year, as estimated by a conservative 59,714 adult respondent survey from the Non-Medical Use of Prescription Drugs (NMURx) Program. Per estimates by the American Kratom Association, it could be used by as many as 16 million people given that 1,950 metric tons of raw kratom product is shipped to the US annually, and the estimated average daily consumption is only 4–6 g [36,37].

Kratom is anecdotally touted (1) to prevent or attenuate opioid withdrawal symptoms when traditional opioids cannot be acquired (a bridge between opioid uses) [38,39], (2) as a replacement therapy for traditional opioids [40], (3) to treat polydrug users that are co-using an opioid, stimulant, alcohol, or other CNS depressant to reduce withdrawal symptoms, or (4) to treat acute or chronic pain (including pain due to trigeminal neuralgia, fibromyalgia, headache, and collagen vascular diseases), depressive and anxiety disorders, and for post-traumatic stress and attention deficit and hyperactivity disorder [41,42]. While kratom case reports are plentiful on online platforms, ambiguities and omissions of important case features (temporal relationship, confounders, and the results of a dechallenge or rechallenge) make determining causality difficult [39].

In this section, we will explore randomized controlled trials and human studies that assess the role of kratom in pain disorders and substance use disorders.

4.1. Kratom's role in treating pain disorders

The acute effect of kratom on pain tolerance via a cold pressor test was assessed in a randomized, placebo-controlled, double-blind study by Vicknasingham et al. [43] During a 1-day inpatient stay, participants (n = 26 males, 24.3 ± 3.4 years, 6.1 ± 3.2 years of chronic kratom exposure) were randomized

to receive kratom and placebo decoctions matched for taste and appearance. The plasma C_{max} concentrations of mitragynine after participants took kratom were between 1500 and 2000 ng/mL. Pain tolerance was assessed before and 1 h after the ingestion of kratom or placebo and measured as time between pain onset and hand withdrawal from an ice bath (point of unbearable pain). Participants in the experimental group lasted a mean of 11.2 ± 6.7 s before using kratom that day and 24.9 ± 39.4 s 1-hour after kratom consumption ($p = 0.02$). In the control group, participants lasted a mean of 15.0 ± 19.0 s before and 12.0 ± 8.1 s after placebo consumption ($p = 0.40$). The study does not assess the onset of analgesic action or the duration of effect but evaluated the impact at a time approximating the C_{max} concentration. It is unfortunate that with the high utilization of kratom, there are not more randomized controlled trials evaluating its efficacy and safety on pain and substance use disorders. Because of the lack of randomized controlled trial data, the Agency for Healthcare Research and Quality has determined that kratom has insufficient evidence to determine its efficacy and safety for pain management [44].

Since mitragynine and 7-hydroxymitragynine interact with opioid receptors, albeit potentially in a manner different from traditional opioids like morphine and oxycodone by acting as G-protein coupled biased partial agonists without activating the β-arrestin-2 pathway [45], it is not surprising that the length of time that participants could retain their hand in the ice water bath was increased after using kratom. However, this randomized controlled trial additionally suggests that kratom, like traditional opioids, may also induce or propagate hyperalgesia (the increased generalized susceptibility to experiencing pain). Oaks et al. assessed 254 chronic pain patients (almost all were chronic traditional opioid users) and 46 non-opioid using controls [46]. The initial time to ice bath hand withdrawal was 43.5 ± 4.4 in the chronic traditional opioid using group and 112.5 ± 97 s in the control group ($p < 0.001$). In the subset of chronic pain patients who had completed opioid detoxification, the time to ice bath hand withdrawal was increased from 25.1 ± 4.3 at baseline to 46.6 ± 6.7 after 31 weeks and then to 50.3 ± 13.4 s after 50 weeks. The control group's longer time to hand withdrawal from the ice bath is similar to McIntyre et al. where a broad section of 1,876 females (54.2, IQR 30.4–116.5 s) and males (82.7, IQR 43.6–150.0 s) were assessed using the cold pressor test. Additional evidence of a hyperalgesic effect associated with chronic kratom use comes from a cross-sectional study of 170 males where abstinence led to people experiencing high rates of moderate-to-severe pain intensity and pain interference, according to the Brief Pain Inventory.

4.2. Kratom's role in substance use disorder

There are no randomized controlled trials assessing the role of kratom in opioid use disorder or other substance use disorders. As such, there is insufficient evidence to determine kratom's relative value versus opioid agonist therapies including buprenorphine or methadone.

Several studies that assess kratom as an intermittent or chronic substitute for illicit traditional opioid use can inform clinicians. Some of these assessed the substitution of kratom for regular opioid use, either for prevention of opioid withdrawal symptoms or as a longer-term substitute for traditional opioids. In a cross-sectional study by Singh et al., 204 current kratom users (142 with current opioid use vs. 62 with past opioid use) in Malaysia were assessed for their major reason for kratom use [47]. While both current and former opioid users reported using kratom to ameliorate opioid withdrawal, current users had a significantly higher likelihood of using kratom for that purpose [OR: 5.4 (95% CI: 2.81–10.18), $p < 0.0001$]. In contrast, former opioid users were more likely to be using kratom for its euphoric (mood elevating) effects [OR: 1.9 (95% CI: 1.04–3.50), $p < 0.035$]. There were no significant differences in the duration [OR: 1.1 (95% CI: 0.62–2.03), $p < 0.708$], daily quantity [OR: 1.5 (95% CI: 0.85–2.82), $p < 0.154$], or frequency [OR: 1.1 (0.62–2.06), $p < 0.680$] of kratom use between current and former opioid users. The standard utilization of kratom in the survey was about 900 mL of kratom daily (the equivalent of 170.19 mg of mitragynine). In a cross-sectional study by Saref et al., 163 participants with a history of illicit opioid use and current kratom use (approximately 214.29 mg of mitragynine daily) were recruited in Malaysia [48]. Participants reported that kratom initiation was associated with decreased respiratory depression, constipation, physical pain, insomnia, depression, loss of appetite, craving, decreased sexual performance, weight loss, and fatigue versus opioid use. Two of the studies were specifically focused on HIV risk behaviors. In the first cross-sectional study of kratom use by Saref et al., 260 participants with a history of illicit drug use and a current use of kratom were assessed [49]. Participants reported a reduction in the illicit use of heroin, methamphetamine, amphetamine, cannabis, benzodiazepines, ketamine, methadone, and alcohol after kratom initiation and a reduction in HIV risk behaviors such as injecting illicit drugs and sharing needles and syringes. In the second study of 32 HIV positive users in Malaysia by Singh et al., there was a reduction in injecting illicit opioids (including heroin) and in sharing syringes and needles in people using kratom [50].

5. Use pattern surveys

Kratom consumption has increased in the United States (US) and other Western countries over the past decade, and estimates ranging from less than 1% to 6% of the general US population have used kratom in the past year. However, this estimate may be low, and better reporting data on actual consumption is needed [5,36,51–53]. Some of the variance in prevalence rates can be attributed to differences in sampling methods, geographical regions, and evolving patterns of use [54,55].

Despite the demographics of kratom users varying across studies, trends have emerged. Most users tend to be White males ranging in age from late teens to middle-aged adults, with at least some college education, and employed [4,6,56,57]. [However, in recent years, there appears to be an equalization between the sexes among younger age groups which may explain that kratom use among females is increasing and may be influenced by the preparation (e.g. more

palatable tea bag or edible preparations vs. concentrates or powders) [4,53,54].

Kratom users exhibit diverse educational backgrounds, with a mix of high school graduates, college attendees, and graduates [40,53,55,57]. Some users perceive kratom as a tool to enhance cognitive performance or manage stress, potentially influencing its appeal among students and working professionals [58]. Employment status among kratom users is variable, with a majority being full-time employed. Some use kratom to manage work-related stress, while others use it to cope with chronic pain or other medical and psychiatric conditions [4,40,53,56,57,55,59]. The variable employment demographics suggest kratom may serve different functions for users.

Understanding why individuals use kratom is crucial for assessing its potential benefits and risks. The motivations behind kratom consumption appear multifaceted and include pain management, mood enhancement, and opioid withdrawal management as key reasons for kratom use [40,53,55,56,60]. Additionally, recreational use and curiosity were reported by some individuals.

Kratom users exhibit a wide range of consumption patterns, including frequency, dose, and mode of administration. Dosage varies substantially, with some individuals taking small amounts to manage health-related symptoms and others consuming higher doses for more pronounced psychoactive effects [57,61]. In the US, kratom is most commonly consumed in a powdered form in capsules or mixed with liquids or as an extract (liquid or lyophilized), since access to fresh leaves is limited.

The safety profile of kratom remains a subject of debate. While some users report beneficial effects, including pain relief and improved mood, concerns have been raised about potential risks. Kratom's analgesic properties are touted to justify its use among individuals seeking relief from chronic pain, who may view it as a substitute for prescription opioids [4,53,55,57,60,61]. Kratom is also used for improvement of psychiatric conditions, such as depression and anxiety, and mood-enhancing effects, including increased sociability and euphoria [4,40,55–57]. These effects on psychiatric conditions can attract recreational users as well as those seeking relief [62]. A subset of kratom users seek cognitive enhancement, using products to improve focus and productivity [53,58]. This motivation aligns with reports of students and professionals using kratom to enhance cognitive performance and potentially improve attention deficit and hyperactivity disorder. Another benefit reported by kratom users is as a potential harm reduction tool for individuals with opioid use disorder [38,57,59,62]. Survey data reveal a significant proportion of users consume kratom to alleviate opioid withdrawal symptoms and reduce cravings [38,53,55,56].

Research suggests that individuals with a history of opioid use are more likely to use kratom for pain management or to alleviate withdrawal symptoms [53]. This raises questions about the role of kratom in the broader opioid epidemic and its potential to perpetuate or mitigate opioid dependence. To further muddy the waters, some but not all kratom users continue to co-use opioids [61].

Survey studies consistently highlight the potential for kratom dependence and withdrawal symptoms, with users reporting tolerance and physical dependence [4,40,57,61,63,64]. Dependence appears more common among individuals using kratom for pain management or as an opioid substitute, but the dose and regularity of use do not correlate to the risk of tolerance and physical dependence in a straightforward way [61].

As discussed in the next section, kratom use has been linked to a range of adverse health effects, including gastrointestinal upset and nausea, altered mental status, agitation, central nervous system depression, tachycardia, liver toxicity, seizures, and death [6,37,56,57,65]. Survey data underscore the need for further research into kratom's safety profile and potential long-term health risks because the outcomes, both beneficial and harmful, are not often linked to the dose or regularity of consumption.

6. Clinical toxicology

The question of kratom toxicity continues to be vexing for many reasons. First, because herbal supplements are largely unregulated in the US, kratom products are often accidentally contaminated or deliberately adulterated with other substances that may be toxic on their own or when mixed together with kratom [66–68]. Second, it is common for kratom users to purposely take kratom together with other psychoactive substances, thereby creating a risk for synergistic drug interactions that can cause adverse events and death [41,69,70]. When more comprehensive toxicology studies are performed on biological samples of alleged kratom-only deaths, other co-ingestants are routinely found that could have caused or contributed to the death [70–72].

Thus, product contamination or adulteration and polysubstance use may be significant sources of kratom-associated toxicity, even if all kratom alkaloids themselves were completely harmless. However, this does not discount the possibility of toxicity due to kratom alkaloids as well. Several mechanisms for such toxicity have been proposed, including opioidergic, adrenergic, or serotonergic effects, human ether-a-go-go (hERG) potassium channel blockade, and hepatotoxicity in susceptible individuals.

6.1. Opioidergic effects

The kratom alkaloids studied most extensively for their μ opioid receptor (MOR) activity are the most abundant alkaloid mitragynine [8], and the most potent MOR agonist 7-hydroxymitragynine [21]. Evidence supporting MOR agonism by these alkaloids comes from in silico, in vitro, in vivo animal and human, and forensic studies. The FDA's molecular docking modeling found that 22 of 25 kratom compounds tested, including mitragynine and 7-hydroxymitragynine, bind to opioid receptors with similar affinities as pharmaceutical opioids [73,74]. These computer modeling results confirmed the in vitro study findings detailed previously that mitragynine is a weak partial agonist at MOR ($K_i = 709$ nM), while 7-hydroxymitragynine is a potent biased or partial MOR agonist ($K_i = 77.9$ nM) [16,45,75]. They are also consistent with the

previously discussed animal and human study results that kratom alkaloids attenuate nociception/pain [43,76,77] and are associated with potential reinforcing behavior/addiction [78–80].

A few forensic cases of opioid-like deaths with lung congestion and high postmortem mitragynine blood concentrations with no obvious alternative causes of death have now been reported [81–83]. There is also an anecdotal report of naloxone being successfully used to reverse kratom intoxication [84]. Taken together, the evidence suggests that high enough doses of kratom alkaloids may cause opioid toxicity via the usual opioid-receptor pathways implicated in conventional opioid overdoses.

6.2. Adrenergic and serotonergic effects

Although it is commonly stated in the literature that kratom has stimulatory effects at low doses and opioid effects at high doses [85,86], both stimulatory and opioid effects can co-occur at any dose [64,87,88]. It is unclear whether kratom alkaloids can sufficiently stimulate adrenergic receptors to cause sympathomimetic toxicity. Literature reports of kratom-associated seizures, psychosis, and other possible stimulant toxicity generally occur in the context of mental illness such as schizophrenia or polysubstance use with other stimulants [89–91], confounding attempts to attribute the role of kratom. Notably, no increased incidence of psychosis was reported in a Malaysian study of chronic kratom users [92]. However, given that the adrenergic effects of kratom alkaloids may be synergistic with amphetamine derivatives and other stimulants, it is reasonable to warn patients with a history of seizure disorder or psychotic mental illness that kratom use may increase their risk of decompensation.

The possible role of serotonergic excess in kratom toxicity has been much less well studied. The few case reports alleging kratom-associated serotonin syndrome all involved multiple serotonergic agents [93–95], such that serotonergic signs cannot clearly be attributed to kratom. Although there is preclinical evidence consistent with serotonergic activity of some kratom alkaloids [12], along with anecdotal clinical reports that could be consistent with serotonergic effects of kratom in humans [87], further research is needed.

6.3. Potassium channel blockade/cardiotoxicity

Inhibition of hERG potassium channels as a potential kratom toxicity mechanism has not been fully explored. hERG channel inhibition can cause QTc prolongation, torsades de pointe, and sudden death [96], and mitragynine inhibits these channels in vitro [97,98]. Although some case reports of suspected kratom-associated cardiotoxicity have been published [99–102], and a small case series found that higher doses of kratom were associated with mild QTc prolongation up to 472 ms [103], no clear-cut examples of kratom-associated torsades have been documented. The only study of kratom cardiac effects in humans found that kratom use was associated with sinus tachycardia, but not QTc prolongation or torsades [104].

6.4. Metabolic enzyme blockade/hepatotoxicity

Drug-induced liver injury (DILI) is thought to occur in susceptible individuals due to a complex interaction between innate patient factors likely involving the immune system, along with the patient receiving a high enough drug dose to trigger hepatotoxic effects [105]. Several dozen kratom-associated DILI cases have been reported in the literature, to the FDA, and to the DILI Network [106,107]. These cases tend to be of a mixed cholestatic and hepatocellular character [106]. The mechanism of possible kratom alkaloid hepatotoxicity is not well understood, but may include any or a combination of factors including pregnane X receptor activation increasing toxic metabolite formation, or inhibition of UDP glucuronosyltransferases, glutathione S-transferases, cytochrome P450 enzymes, and P-glycoprotein [107].

6.5. Product dosing

Finally, no toxicologic discussion of kratom would be complete without consideration of the role of product concentration on toxicity. The fundamental maxim of toxicology that 'the dose makes the poison' applies to kratom alkaloids as with all substances [108]. Because kratom is not FDA-approved for any therapeutic use and there are limited safety trials of kratom alkaloids in humans, we do not yet have a good understanding of what might be a therapeutic dose versus a toxic dose of kratom. Thus, individual consumers are left to guess regarding what kratom doses to take and how often to take them. Such an uncontrolled self-experimentation is becoming more problematic given the increased availability of kratom extracts, which are highly concentrated, more palatable solutions of kratom alkaloids [109]. Use of such products further increases the risk of overdose and toxicity from kratom alkaloids, particularly when they are mixed with other psychoactive substances.

7. Abuse potential & kratom use disorder (KUD)

The human abuse potential of kratom and its alkaloids remains poorly understood. Although preclinical work has found that kratom's major alkaloid, mitragynine, shows some indicators of abuse potential, the findings remain mixed [110]. While mitragynine has been demonstrated to produce indicators of dependence, it shows a relatively low abuse potential when compared to its active metabolite, 7-hydroxymitragynine, and when compared to substances with reinforcing effects, such as heroin, morphine, or methamphetamine [19,85,111–115]. For instance, in one study, mice treated with a kratom alkaloid extract, mitragynine, or mitragynine pseudoindoxyl, a metabolite of mitragynine, under multiple conditions evinced significantly fewer signs of precipitated withdrawal when administered naloxone and showed less dependence than control mice receiving morphine [116]. Though far from conclusive, evidence is converging to indicate that mitragynine has some therapeutic potential in reducing self-administration of addictive substances such as morphine or heroin [113,114]. However, preclinical work does not necessarily translate to humans given that people are consuming

various products ranging from whole leaf plant material to extracted alkaloids, which can include isolated and concentrated forms. In the case of whole leaf, there is a mixture of alkaloids acting on multiple receptor systems for which the in vivo pharmacology remains poorly understood [26,117]. The abuse liability of whole leaf commercial kratom products, which are those commonly consumed by humans, remains largely unknown. Presently, the most practical understanding of the potential for kratom use to develop into dependence or addiction comes from the self-report of people who consume it regularly at self-selected doses.

Although data remain limited, there is a nascent body of evidence that both the botanical kratom and the products derived from it can result in physical dependence, clinically defined as the presence of tolerance and withdrawal symptoms. Kratom tolerance and withdrawal symptoms have been documented in Southeast Asia and in Western countries, but data remain scarce [53,57,81,118–120]. Indeed, most of what is known about kratom dependence or addiction has come from self-report or case reports which often lack sufficient detail of assessment methods or outcomes [121–126]. Although kratom dependence among regular kratom consumers who reside in regions where kratom is indigenous is increasingly assessed, it is difficult to make comparisons to kratom consumers in Western nations due to the variability and differences of kratom preparations or products consumed [127–129].

Kratom adverse effects, including dependence, appear more likely to occur when kratom is used regularly for a longer period of time and at higher amounts [61,81,118,130]. Although speculative, extract products, which are perceived as more potent by consumers, may result in tolerance that develops more rapidly compared to whole leaf kratom products that have been reported to result in the development of tolerance, but more gradually [87,109,123]. Little is known about the development and progression of kratom tolerance; however, some US consumers describe it as slow to develop and largely manageable [87,123]. For example, consumers who use regularly will take scheduled 'tolerance breaks' in order to help 'reset' their tolerance; they will also mix products or strains obtained from different vendors or rotate among different brands during periods of use in order to diversify what they are consuming and thus, potentially, slow the onset of tolerance to one particular strain [87,131]. Although some have reported decreasing their typical kratom dose following use initiation, others have reported increasing their dose amount over time, which is indicative of tolerance [61].

Withdrawal from kratom has been documented in the case report literature, but there are few cases published, and among those that are, validated assessment methods are rarely provided [125]. Kratom withdrawal has been assessed using the Subjective Opioid Withdrawal Scale (SOWS) or Clinical Opioid Withdrawal Scale [125], though kratom alkaloids act on many other systems other than the opioid system. Both case reports and survey self-report SOWS scores (when applied to kratom) suggest that kratom withdrawal symptoms are generally mild to moderate and of a short duration [53,132,133]. Symptoms associated with kratom cessation and/or withdrawal include craving for kratom or another substance, anxiety, difficulty sleeping, depression, fatigue, restlessness, restless legs, irritability, and body aches. In one direct-observation pilot study in which 10 adults who regularly use kratom were asked to refrain from using their typical morning dose of kratom prior to their study session which involved kratom self-administration, SOWS scores were consistent with mild withdrawal (1–10); however, even after kratom self-administration, only two participants reached non-zero scores, reflecting the non-specificity of some SOWS items, such as anxiety [134]. This underscores the need to assess kratom withdrawal using multiple assessment tools, potentially including those used for caffeine, nicotine, or substances other than opioids, given kratom's complex pharmacology.

Although kratom-related dependence (e.g. tolerance, withdrawal) has been established in the literature, kratom addiction has been less well studied. Using DSM-5 diagnostic criteria for substance use disorder (SUD), which provides a clinically recognized method for assessing the presence and severity of both dependence and disordered use, kratom addiction has been found across two US-based surveys to be primarily mild [53,119]. Few DSM-5 SUD assessments for kratom (i.e. kratom use disorder, [KUD]) or other validated assessments for kratom addiction have been reported in the medical literature, and often these lack critical details such as severity and symptomatology [125,126]. In one small survey that assessed KUD, individual symptoms primarily reflected tolerance and withdrawal; however, other common symptoms included using more than intended, unsuccessful quit attempts, and cravings [119]. Qualitative data suggest that perceived kratom addiction is reported by some with long use histories, but with the caveat that even among these reports, physical dependence is often discussed interchangeably with addiction. These discussions also occur in the context of kratom being used with reported benefit that outweighs dependence and/or addiction [87,123]. Such reports make it challenging to fully characterize the phenomenon of KUD. For instance, some self-reports among regular consumers indicate that kratom has adverse effects related to dependence or is perceived as habit-forming; however, these conceptualizations are endorsed at lower rates than more favorable conceptualizations, such that kratom is helpful, therapeutic, safer than other substances, should be legal, or is a benefit rather than a hindrance to daily living [60,61]. Likewise, the psychosocial functioning of kratom consumers appears to be largely intact, even in the presence of symptoms related to dependence [53,87,119,135].

Presently, the absence of hazardous kratom use and continued use despite adverse consequences, which are hallmarks of addiction, coupled with the lack of impairments in psychosocial functioning when KUD or dependence as assessed among chronic consumers, makes it difficult to draw firm conclusions about kratom's abuse liability. That kratom dependence is reported by consumers who also perceive the benefits of kratom makes the public health implications of widespread kratom use truly unknown. Understanding KUD must be a goal for clinical researchers moving forward. In the meantime, current data suggest that prolonged and regular use of kratom at high doses should be expected to result in a mild-to-moderate physical dependence.

8. Discussion

The rapid growth of research surrounding kratom in recent years is an indicator both of its popularity among those using it and the potential therapeutic and detrimental effects of its use. While traditional use dates back at least a century in Southeast Asia, the rapid availability of varying kratom formulations and products in the US and globally cannot be directly compared to the ethnobotanical use of fresh leaf material. Even the assumption that most of the pharmacological effects of kratom are associated with mitragynine should be critically evaluated. Mitragynine remains the kratom alkaloid most studied and is associated with effects mediated through partial agonist activity at μ-opioid and adrenergic receptors. However, the alkaloids speciogynine and paynantheine interact strongly with serotonin receptors, which may explain the self-reported use of kratom for depressive and anxiety symptoms. Case reports involving kratom also provide some indication that adrenergic and serotonergic actions may contribute to antinociceptive effects and cardiovascular and CNS toxicity.

The limitation of clinical kratom research remains a dearth of controlled clinical trials, with user surveys presenting a reporting bias toward beneficial effects, and clinical case presentations biased toward describing adverse events of kratom use. The variability of kratom products and dosing and unstandardized reports of co-use with other substances hinder a direct comparison of cases or even among survey respondents.

Other barriers to reaching a consensus about kratom effects include that there is no consensus among clinicians regarding the definition of kratom use disorder, variability in product composition, potential contamination or adulteration of kratom products, dosing and frequency inconsistencies, and the absence of a federal regulatory framework for kratom in the US. The lack of regulation creates a market that may lead to increased occurrence of tolerance and development, especially for products like extracts that contain a higher total alkaloid content than what naturally occurs in native leaf material [109].

9. Expert opinion

The multifaceted use of kratom products in the US and other countries can be distinguished from the traditional use of fresh leaf material in its native Southeast Asia. While the kratom alkaloid mitragynine remains the predominant focus of scientific investigations, the contribution of other alkaloids to the complex pharmacology of kratom is gaining recognition and supports the notion that kratom is unlike classical opioids and should be viewed in the context of polypharmacology. One advantage of kratom as a potential therapeutic treatment is the partial opioid agonist activity of several kratom alkaloids in conjunction with their activity at adrenergic and serotonergic receptors. The opioid and serotonin agonism provides analgesic benefits, while the adrenergic activity may function similar to clonidine in the treatment of opioid use disorder. This dual activity remains to be evaluated in clinical trials.

It is clear that kratom consumption is associated with risks that appear to be dose- and frequency-dependent as well as linked to polysubstance use and comorbid conditions. Though many survey reports describe the adverse effects of kratom as primarily gastrointestinal in nature, rare and severe adverse events may include hepato- and cardiotoxicity that should warratn caution regarding the use of kratom by patients with related preexisting conditions. No clinical data are available to date regarding dosing and frequency of use, although survey reports indicate that three daily doses of up to 5 g native kratom leaf material are associated with substantially lower risk of adverse effects than higher doses and more frequent use. Concentrated formulations and kratom extracts may expose a user to higher concentrations of alkaloids with potential toxic effects.

The therapeutic benefits of kratom remain to be further elucidated in controlled clinical trials. Pre-clinical animal models point to possible use of kratom in mitigating substance use disorder withdrawal symptoms, not only for opioids but also stimulants. Given that there are currently no medications to treat stimulant use disorder, kratom may provide a promising drug development lead for this condition. Among kratom alkaloids, although mitragynine remains the primary alkaloid of study, some of its structurally closely related isomers may prove to be more pertinent sources of kratom pharmacology. The utilization of mitragynine and its derivatives as structural lead compounds in the development of a new chemical class that can be evaluated for a range of pharmacological effects remains intriguing.

Clinicians working with patients who are consuming kratom should be aware of the diversity of use motivations, inquire about intended use and perceived benefits, and monitor the dose and frequency of use to limit potential adverse effects. The potential for drug interactions with any prescribed or over-the-counter medications that are substrates for CYP2D6 and CYP3A4 should be evaluated. Although an open recommendation to use kratom should not be made, given the lack of proof of its efficacy for any medical condition, inquiring and counseling a patient who uses kratom is essential to reduce the risk of adverse effects.

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