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REVIEW

A Review of Kratom Product Evolution and Its Associated Health Outcomes

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Purpose of Review: Kratom (*Mitragyna speciosa* Korth) is a tree that belongs to the coffee family (Rubiaceae) and is native to Southeast Asia. This review article focuses on the diversification of kratom products, differentiating between native leaf, extracts and isolates based on use patterns and conceptualization of kratom for self-treatment of disorders.

Findings: The dried powdered native leaf and its extract derivatives are primarily used as kratom products in the US and Europe. Diversification of kratom products has increased since 2021 following the global COVID-19 pandemic. There has been a rise in chemically altered kratom products, including enriched extracts, edibles, resins, and isolates. Most prominent among them is the oxidative metabolite of mitragynine, 7-hydroxymitragynine.

Summary: The total alkaloid content is lowest in native kratom leaf products (2–5% by weight) which is associated with a lower potential for adverse effects and dependence compared to concentrated products, where extracts can contain five to 50 times the alkaloid content of the native leaf. Purified compounds, predominantly mitragynine and semi-synthetic 7-hydroxymitragynine, are likely to be associated with a higher risk for dependence and overdose potential.

Keywords: kratom, safety, public health, 7-hydroxymitragynine, mitragynine

Introduction

Kratom (*Mitragyna speciosa* Korth, Rubiaceae) is a tree that belongs to the coffee family that originated in Southeast Asia. Kratom has been available in the US for at least two decades, likely longer as a specialty grown tree in the Southeast United States.[1,2] As the global market for kratom continues to expand, so too does the diversity of the products derived from the kratom plant. Kratom is mainly consumed in Southeast Asia by chewing the fresh leaves of the tree or preparing a tea decoction. Kratom is traditionally used as a treatment for alleviating pain, reducing fatigue, improving gastrointestinal conditions, and reducing fever.[2,3]

There are reports of increasing diversification of kratom in its related uses, such as self-treatment of mood disorders, which includes depression, anxiety, post-traumatic stress disorders, enhanced focus, and boosting energy levels.[4]

For centuries, kratom has been used in the form of native leaves. Recently, kratom has been widely diversified and made commercially available in concentrated extracts, isolates, edibles, capsules, and tea bag preparations. The potency of kratom depends on the formulation. Studies have shown that the onset of action of capsules and extract powders are faster in comparison to tea bag preparations and loose powder.[5] Extract powders and capsules can contain higher amounts of alkaloids and allow for the ingestion of larger quantities to circumvent the unpleasant and bitter taste of the leaf.[6]

Kratom contains a complex mixture of over 40 identified alkaloids.[3] The primary alkaloids responsible for the effects of kratom are the indole alkaloids mitragynine, which accounts for 60–70% of total alkaloid content, and corynantheidine.[7] While 7-hydroxymitragynine, the active metabolite of mitragynine, is more potent at opioid receptors, it is not found in fresh native kratom leaf but rather the result of oxidative metabolism during the drying process.[8] In addition, the stereoenantiomer of mitragynine, speciociliatine, acts on adrenergic receptors while paynantheine has been shown to activate serotonin receptors.[8]

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This review provides a summary of the diversification of kratom products. A discussion of the differences between native leaves, extracts, and isolates for substance abuse and rehabilitation is provided as dependence risk with kratom product use has evolved.

Diversity of Kratom Products

Kratom has been increasingly commercialized in the US and globally over the past decade. In Southeast Asia, kratom is consumed directly or brewed into tea from its fresh leaves. However, dried leaf products can be transported easier, are usable for extended periods, and are more popular in other countries.[9]

While the dried powder formulation of kratom remains the primary product in the US, other formulations have emerged such as capsules, edibles, tablets, gummies, liquid shots and vaping products. The increasing diversity of kratom products mirrors that of the commercial cannabis market.

The move towards diversification is fueled by perceived benefits, such as potency and consistency, versatility, reliable effects, and consumer demands.[10] The concentrated alkaloid in consumer-friendly formulations offers more predictable effects in comparison to the variable leaf composition. Diversification allows research and development to focus on specific alkaloids as well as their properties. Different formulations meet the market's desire for more potent and convenient products.

Kratom diversification has increased since 2021 following the global COVID-19 pandemic.[11] The different perceived and reported effects of kratom products are at least in part dependent on the product formulation. A study found that extract powders and capsules present with a faster onset of action and stronger effects compared to native kratom leaf powder while also showing higher variability of dosing within users.[12]

As the number of kratom products is rapidly growing, many of them are available in dosage forms further removed from traditional use, where more research is still needed to assess the pharmacokinetic and pharmacodynamic differences between dosage forms. Some dosage forms, in particular liquid shots and edibles, may present with an even faster absorption and onset of effects given that the alkaloids are dissolved and can easier penetrate through cellular barriers. The bioavailability of mitragynine in humans is estimated to be approximately 30% following oral ingestion.[13]

Kratom Pharmacology

Even though there have been more than 40 structurally related indole and oxindole alkaloids identified in kratom, the indole alkaloid mitragynine was the first alkaloid to be isolated from the leaves.[14] Subsequently, other alkaloids including mitragynine's diastereomers speciogynine, speciociliatine and mitraciliatine, have been identified.[14] Mitragynine is the most prevalent in fresh kratom leaves accounting for up to 2% of native kratom preparations by mass and 40–66% of the total alkaloid content.[8] Mitragynine is metabolized to 7-hydroxymitragynine (7-OH) and 9-O-demethylmitragynine in the human liver.[8]

7-hydroxymitragynine is found in minor amounts in some US kratom products, but it is likely to be generated through oxidative metabolism while the fresh leaves are being processed into dried formulations.[15]

Mitragynine exerts partial agonist action at the μ-opioid receptors with a lower binding affinity than morphine. Interestingly, 7-hydroxymitragynine is more potent at the μ-opioid receptors than morphine.[16] However, naturally occurring amounts of 7-hydroxymitragynine are likely insufficient to generate a substantial pharmacological effect. There has been a substantial amount of research conducted to prove the interactions between mitragynine and related alkaloids with receptors in the central nervous system as discussed below.[17]

Opioidergic Effects

Studies conducted in rodents and humans found that kratom preparations, alkaloid-enriched extracts, and pure mitragynine presented central analgesic activity which was fully antagonized by non-selective opioid antagonists such as naloxone.[16]

Mitragynine as well as 7-hydroxymitragynine, corynantheidine, speciociliatine and mitragynine pseudoindoxyl interact with μ-opioid receptors. These indole and oxindole alkaloids vary in their receptor binding affinities and subsequent relative potencies. Mitragynine was found to be a weak partial opioid agonist with a lower binding affinity

to μ-opioid receptors than morphine. 7-hydroxymitragynine, the hydroxyl metabolite of mitragynine, presents a much greater receptor binding affinity than morphine, almost exclusively acts on opioid receptors, and can substitute for morphine in a rodent dependence model where mitragynine did not display this substitution behavior.[16]

Mitragynine pseudoindoxyl, a metabolite of 7-hydroxymitragynine resulting from metabolism in human plasma, has an even greater potency than 7-hydroxymitragynine. Contrary, corynantheidine (9-demethylated mitragynine), another kratom indole alkaloid, was found to be a selective μ-opioid receptor antagonist. Speciociliatine was found to act on the μ-opioid receptor as a partial agonist with lower potency than 7-hydroxymitragynine.[18]

Adrenergic Effects

Several kratom alkaloids act on adrenergic receptors and have been shown to reduce pain and opioid withdrawal symptoms.[19] This explains the reported stimulant effects of mitragynine and other related alkaloids. Preliminary information on the specific binding affinities of mitragynine and other related kratom alkaloids to adrenergic receptors indicates diverse actions.

Studies found that mitragynine has moderate and non-selective binding affinities at alpha-1A, 1B and 1D, and alpha-2A, 2B and 2C receptors.[20,21] 7-hydroxymitragynine, however, had no binding affinity to adrenergic receptors and to date shows only selectivity for opioid receptors.[19]

Corynantheidine was found to have high and selective binding affinity at alpha-1D but not alpha-2 adrenergic receptors.[22]

Speciogynine showed non-selective binding affinities for alpha-2A, 2B, and 2C receptors similar to mitragynine, likely contributing to kratom's antinociceptive effect in a manner similar to clonidine which has become a treatment option in opioid-induced withdrawal.[18]

Serotonergic Effects

Serotonin receptors are involved in regulating physiological functions such as cognition, mood, autonomic system function, and sleep. Pre-clinical research studies in rodents showed that mitragynine, like ritaserin, acts as a competitive antagonist at 5-HT_{2A} receptors.[23]

As a result, it has a suppressive effect on the central serotonin neurotransmission system. Other related alkaloids such as speciogynine, speciociliatine and paynantheine interact with the 5-HT_{1A} receptor as partial agonists which may explain the traditional use of kratom as a mood enhancer.[23]

There have also been case reports of serotonergic toxicity and associated adverse effects with the ingestion of large doses of kratom or kratom derived products, in particular extracts.[24]

Dopaminergic Effects

Mitragynine has shown antipsychotic, antidepressant, anxiolytic and anti-addiction effects in rodent studies as well as observational studies in humans.[25]

Pre-clinical studies have demonstrated binding affinity of mitragynine to dopamine receptors, specifically the D_2 receptor.[25]

Mitragynine may exert its anxiolytic-like activity in part through D_1 and D_2 receptors as a moderate dopamine agonist whereas other studies indicated that a kratom leaf extract exhibited an antipsychotic-like effect in mice by blocking the central D_2 receptor.[25] Other kratom alkaloids may explain the diverse actions resulting in a complex pharmacology.

Pharmacokinetics and Drug–Drug Interactions

Kratom alkaloids have been studied both as individual compounds and as complex mixtures in the form of kratom tea or similar extractions for in vitro and in vivo pharmacokinetics. Systemic exposure to kratom alkaloids was higher in one human study when administered as a kratom tea or an organic extract compared to individual compounds.[26] A single oral dose of kratom (2 g) tea containing defined amounts of mitragynine, speciogynine, paynantheine, speciociliatine, isopaynantheine, and mitraciliatine was administered to six healthy volunteers and concentrations were quantified in plasma up to 96h post-dose. 7-hydroxymitragynine, a potent and minor metabolite of mitragynine, was also quantified.

Mitragynine and paynantheine, the most prominent alkaloids, presented with fast absorption and peak plasma concentrations after 1 hour (T_{max}).[26] Conversely, delayed absorption was observed for mitraciliatine and isopaynantheine with T_{max} of 4.5-hours. Speciogynine and speciociliatine, two enantiomers of mitragynine, showed T_{max} concentrations of 2 and 2.5 hours, respectively.[26]

The distribution of kratom alkaloids followed their stereochemistry with 3S isomers, namely mitragynine, speciogynine and paynantheine following a two-compartmental model, whereas the 3R isomers mitraciliatine, speciociliatine and isopaynantheine exhibited monophasic distribution in humans.[27] All kratom alkaloids displayed high protein binding (>90%) in human plasma with blood-to-plasma ratios ranging from 0.65 to 1.05.

The dose-normalized systemic exposure (AUC/Dose) after an oral dose of kratom tea revealed that mitraciliatine showed the highest systemic exposure followed by isopaynantheine, speciociliatine, speciogynine, paynantheine and mitragynine.[27] While mitraciliatine is present in lower amounts in native kratom leaf, its AUC/Dose was 90.5-fold higher than mitragynine and an elimination half-life of 17.8 hr. This higher systemic exposure to mitriciliatine may relate to a differential pharmacological effect profile of kratom leaf compared to pure mitragynine or 7-hydroxymitragynine preparations.

Mitragynine is predominantly metabolized by CYP 3A4 with minor pathways involving CYP 2D6 and CYP 2C9 to the primary mono-oxidized and demethylated metabolites, mitragynine carboxylic acid and 9-hydroxycorynantheidine.[28]

Speciociliatine is also primarily metabolized by CYP 3A4 with minor CYP 2D6 contributions to form a 7-hydroxymetabolite analogous to 7-hydroxymitragynine.[28]

CYP 3A4 is the most abundant Phase 1 enzyme in both the intestine and liver serving as first-pass metabolism for kratom alkaloids. Small portions of kratom alkaloids are excreted unchanged in the urine with the fraction excreted unchanged (f_e) higher for the 3R isomers mitraciliatine, speciociliatine, and isopaynantheine (f_{ex} 0.09–0.1) than for the 3S isomers mitragynine, speciogynine and paynantheine (f_{ex} 0.003–0.016).[28]

While 7-Hydroxymitragynine was not present in a kratom product administered to healthy volunteers in one study, hepatic metabolism from CYP 3A4-mediated oxidation of mitragynine resulted in a metabolite-to-parent AUC ratio of 7-hydroxymitragynine to mitragynine in humans of 26.5%.[29] Although more research is needed, the conclusion is that about one third of mitragynine is metabolized to 7-hydroxymitragynine following oral absorption. Another metabolite resulting from further metabolism of 7-hydroxymitragynine in human plasma is mitragynine pseudoindoxyl.

Metabolism studies have identified several kratom alkaloids as CYP inhibitors using human microsomes, in vitro cell models, and recombinant CYP450 enzymes. Mitragynine and corynantheidine were found to be potent inhibitors of CYP 2D6 in vitro while speciogynine and paynantheine presented with moderated in vitro inhibition of the same enzyme.[29]

While in vitro studies are important, the clinical relevance of enzyme inhibition needs to be tested in humans. A clinical drug interaction study assessed the impact of the metabolic activity of CYP 3A4 and 2D6 using a chemically defined kratom leaf product (2 g kratom tea containing 39 mg mitragynine) in healthy volunteers with dextromethorphan and midazolam as substrate drugs.[17] Midazolam was the probe drug for CYP 3A4 and dextromethorphan for CYP 2D6. In the presence of kratom tea, midazolam peak plasma concentration and the area under the plasma-concentration time profile (AUC) increased 1.5- and 1.4-fold, respectively. Mitragynine is a potent in vivo inhibitor of CYP 3A4, which is responsible for metabolizing many drugs including midazolam, resulting in a clinically impactful increase in the plasma concentration of such drugs with potential for adverse effects. On the other hand, the relatively low dose of kratom (2 g) did not significantly change the pharmacokinetics of the CYP 2D6 substrate dextromethorphan.[17]

High doses of kratom products can potentially result in clinically impactful adverse effects for substrate drugs of CYP 3A4 and CYP 2D6 by inhibiting their metabolism resulting in elevated blood concentrations.

Kratom Use and Physical Dependence

Preclinical work found that mitragynine may lead to dependence. Mitragynine did demonstrate dependence, with lower abuse potential in comparison to its metabolite 7-hydroxymitragynine, as well as other substances such as heroin, morphine, and methamphetamine.[30] Current evidence indicates that mitragynine may have a therapeutic potential as an adjunct or stand-alone therapy in reducing self-administration of other addictive substances such as morphine or heroin.[30]

When people consume native whole leaf kratom material, there is a complex mixture of indole and oxindole alkaloids that act on multiple receptor systems, resulting in diverse and often dose-dependent pharmacological and toxicological effects that are not clearly understood. Kratom's potential for dependence comes primarily from clinical case reports of people who consume kratom regularly. There is evidence that kratom leaf products may result primarily in physical dependence with predominant signs of tolerance and withdrawal symptoms.[30] Extracts/concentrated formulations and semi-synthetic derivatives may be more potent compared to whole leaf kratom products and may present with a higher risk of abuse potential.[31]

A cross-sectional study using a longitudinal smartphone-based ecological momentary assessment (EMA) approach was conducted between July 1 and October 31, 2022 among regular kratom users with at least 3 times weekly use for 4 weeks or longer.[32] The criteria for substance use disorder were based on the 11-question tool of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Among the 357 participants who completed the EMA, motivations for use were mostly for general well-being or management of health conditions. Kratom was rated as being safer than other substances and mostly effective at improving quality of life, boosting energy, replacing opioids and relieving opioid withdrawal. Kratom was used as a long-term or short-term substitute for opioids by many participants. During the daytime, Participants mainly used kratom during the time and titrated their dose and frequency to suit their needs. Participants who were using higher amounts and with higher frequency were more likely to present with withdrawal or tolerance, the primary physical signs of dependence.[33]

Based on the limited available studies, there is a mix of perceived benefits and potential dependence signals with the long-term and high frequency use of kratom. While there are physical dependence signals like cravings, withdrawal, and not being able to reduce kratom use, most kratom users present mild to moderate dependence. Clinical studies examining the differential abuse potential of kratom preparations are still needed.

Connection of Kratom Dependence with Frequency and Quantity

A survey study was conducted to show the average frequency of kratom use and the amount per dose in comparison with the degree of concern for kratom dependence. The survey included 1000 respondents who had used kratom products frequently and asked them to report the product formulation, what symptoms they experienced if they discontinued their use of kratom, whether they changed their frequency of kratom use depending on the product and formulation, and self-reported beneficial and detrimental effects related to their kratom use. The frequency of use per day was 1.8 times for extract powder to 3.4 times for gummies.[34] For extract liquids, tinctures and shots, the lowest average amount per dose was rated as very concerning for dependence development by respondents. In contrast, increased amounts per dose for tea bags, leaf/extract powder, and gummies/capsules/pills were related to increased concern for dependence.[34]

Increasing use frequency of kratom was related to higher risk of adverse effects while less frequent use of leaf powder was associated with more anxiety and irritability and lower frequency of kratom shot consumption was correlated with constipation.[34] For tea bag preparations and gummies, less frequent use was associated with reports of dizziness. More frequent use of kratom shots, extract powders, and extract liquids were associated with sleep disturbances and weight loss. Less frequent use of kratom shots and capsules was associated with sweating. The decreased frequency of kratom shot, or gummy use, was linked to abnormal heart rhythm. The dosage forms that were associated with increased adverse effects such as constipation, nausea, vomiting, sleep disturbances, and sweating were gummies and capsules/pills.[34]

Increased use of leaf/extract powder correlated with constipation and more tea bags led to sweating. Negative correlation was seen between extract liquid and abnormal heart rhythm.[34]

The findings from the survey confirmed an earlier ecological momentary assessment study in 365 participants that were followed for four weeks that frequency rather than dose of kratom use were associated with higher risk of dependence, withdrawal, cravings, and adverse effects.[12,32]

Kratom Use Disorder

Even clinical evidence for the abuse potential of kratom and its alkaloids is lacking in controlled clinical studies, there are preclinical studies that found mitragynine presenting some potential for dependence although it is lower compared to

morphine and 7-hydroxymitragynine. In one study, mice were treated with morphine, mitragynine, or mitragynine pseudoindoxyl and withdrawal induced with naloxone.[35]

Mitragynine resulted in less pronounced withdrawal compared to the other substances. Because mitragynine has been shown to reduce self-administration of substances such as morphine or heroin, there is growing interest in its therapeutic application as an adjunct for the treatment of substance use disorders. The abuse potential of whole leaf kratom products remains unknown but likely requires more frequent and higher amounts of use.[36]

Several studies in animals and human surveys indicate that kratom is utilized to reduce the use of other substances, in particular opioids, stimulants, and alcohol.[37–41] The current findings support the potential development of a kratom product or isolated alkaloid to treat a range of substance use disorders based on the established pharmacology and observational studies. However, controlled clinical trials are needed to confirm the efficacy and safety of kratom for substance use disorder treatment.

There is no formal recognition of kratom use disorder but instead to diagnose an individual with Kratom use disorder, it is essential that there is a continuous pattern that meets DSM-5 diagnostic criteria for substance use disorders. To diagnose kratom use disorder, tolerance or withdrawal alone are not sufficient criteria for diagnosis. There are eleven DSM-5 criteria which are used in evaluating an individual and there have to be at least two criteria within a 12-month period that would substantially cause distress.[42]

When it comes to the treatment of kratom use disorder, there is no established therapeutic approach. The most frequent pharmacotherapy to treat kratom use disorder is based on the primary opioid withdrawal symptoms and utilizes buprenorphine or buprenorphine-naloxone. It has been recommended that when administering buprenorphine, the dosing should be titrated to patients with kratom use disorder based on their clinical responses. If a patient presents with concomitant kratom and opioid use disorder, the first line of treatment should be buprenorphine as well as naltrexone/methadone.[42]

Regular kratom use over a longer period and at higher amounts and frequencies is likely to increase the risk of dependence. Extract products are more potent hence further increasing the risk of tolerance development and subsequent dependence compared to whole leaf products.

Kratom Withdrawal

Kratom withdrawal has been assessed using both the Clinical Opioid Withdrawal Scale (COWS) and Subjective Opioid Withdrawal scale (SOWS).[43,44] When the case reports and SOWS scores were applied to kratom, it presented with mild to moderate withdrawal which was of short duration. Kratom withdrawal symptoms include cravings, anxiety, depression, fatigue, sleep disturbances, and body aches.[45]

In a small pilot study, 10 adults who use kratom regularly were asked to refrain from their morning dose and were subsequently evaluated for withdrawal symptoms and severity.[46] The SOWS scores were consistent with mild withdrawal (1–10) with two participants reaching non-zero scores, which may reflect the non-specificity of some SOWS items, such as anxiety.[33]

Even though kratom-related dependence, such as tolerance and withdrawal, has been documented in the literature, additional research studies such as a human abuse potential study, need to be conducted. Using the general DSM-5 diagnostic criteria for substance use disorder, kratom dependence has been found across two US-based surveys to be mild.[37] There is no officially defined kratom use disorder, and general assessment tools such as the DSM-5 criteria sometimes incompletely assess severity and symptomatology. In another survey that assessed kratom use disorder per DSM-5, tolerance and withdrawal remained the primary symptoms reported. However, other common symptoms include using more than intended and cravings for kratom.[37]

Opioid-like deaths with lung congestion and high postmortem mitragynine blood concentrations have been reported in forensic cases with no clear alternative causes of death.[47] One case of opioid toxicity reported the use of naloxone to successfully reverse kratom intoxication although the specific kratom product was not noted.[47] Current evidence does suggest that high doses of kratom alkaloids may cause toxicity similar to opioids that is at least in part mediated through opioid-receptor pathways.[47]

Clinical Toxicology and Safety of Kratom

Herbal supplements are less strictly regulated in the US, and kratom is not currently recognized by the US Food and Drug Administration (FDA) or any other regulatory agency as a supplement. Some states have not regulated kratom, several other states have imposed laws such as the Kratom Consumer Protection Act on kratom, while others have banned it altogether.[48]

This complicates interpretation of toxicological findings related to kratom because of the potential for product contamination or adulteration with other unknown substances that may be toxic. This may contribute to variability and inaccuracies in reported outcomes. Kratom users may co-use other psychoactive substances, increasing the risk of clinically relevant drug interactions, which can increase the risk of fatality.[30]

Kratom toxicity has been observed through its opioidergic, adrenergic, and serotonergic pharmacodynamics as well as cardiotoxicity and hepatotoxicity.

Several of the kratom alkaloids bind directly to serotonin receptors. Mitragynine has the strongest affinity for the 5-HT_{2B} receptor and moderate affinity for the 5-HT_{1A} and 5-HT_{2A} receptors as an agonist and acts as a competitive antagonist at the 5-HT_{2A} receptor.[49]

Kratom's impact on serotonin levels is dose dependent. Evidence from rat studies showed that low doses of mitragynine caused only minimal changes in serotonin activity in the brain whereas higher doses increased serotonin levels as well as dopamine and GABA significantly.[49] In the same rat study, it was observed that after four consecutive days of high doses of mitragynine there were addictive-like behaviors that were correlated with elevated serotonin and dopamine levels.

There were 13 observational studies that found self-treatment for anxiety, depression, and other mental health conditions as the most common reasons people turn to kratom.[50]

Mitragynine's antagonism at the 5-HT_{2A} and 5-HT_{2C} receptors mirrors that of some antidepressant and antipsychotic drugs. Combining kratom with medications that raise serotonin levels in the synapse, particularly selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or tricyclic antidepressants, creates a potential risk of serotonin syndrome.[51] Serotonin syndrome is a potentially life-threatening condition where excess serotonin causes agitation, rapid heart rate, high blood pressure, and in severe cases, seizures or organ damage. In a small study involving 10 patients, four reported experiencing jitteriness in conjunction with nystagmus and light-headeness that is termed "the wobbles" by users and may resemble initial signs of serotonin toxicity.[52] This was reported after ingestion of a single large dose of kratom products, in most cases extracts or concentrates.

Although there is some evidence consistent with serotonergic activity and toxicity of kratom in clinical case reports, further research is still needed.

There is insufficient evidence of whether kratom alkaloids can sufficiently stimulate adrenergic receptors to cause sympathomimetic toxicity. Literature reports of kratom-associated seizures, psychosis, schizophrenic episodes, and other stimulant toxicity point to a potential involvement of the sympathetic nervous system which can occur in a polysubstance use setting in combination with other stimulants.[53] Kratom combined with amphetamine derivatives or other stimulants in patients who have a history of seizure disorders or psychotic mental illnesses can increase their risk of decompensation.[20] However, it remains unclear whether kratom was contributory or causative in psychosis, hallucinations, and seizures because all of the reports indicate polysubstance exposures with unknown medical history.

Several case reports of drug-induced liver injury (DILI) and hepatotoxicity have been reported in recent years in patients using kratom chronically and in high amounts.[54] The pattern of kratom liver damage is often cholestatic (blocked bile flow) or mixed (involving both bile and hepatocellular inflammation) including elevated liver enzymes, jaundice, abdominal pain/nausea, fatigue, and dark urine.[55] All abnormal liver readings did return to normal following cessation of kratom consumption.

Kratom can potentially induce life-threatening arrhythmias due to interactions of several alkaloids with the heart's electrical conduction system. Laboratory studies have shown that mitragynine inhibits hERG potassium channels which can cause QT interval prolongation, Torsades de pointe and sudden death.[56,57] Patients with pre-existing heart conditions are at greater risk for adverse cardiovascular outcomes from kratom. There was only one observational retrospective study of kratom cardiac effects in humans, where kratom use was associated with transient sinus tachycardia but not QT prolongation or Torsades de pointe.[56]

Kratom Product Regulation

Because kratom and its alkaloids are not categorized as a drug, food or supplement in the US, there is no prescription or over-the counter drug product containing kratom or its alkaloids that are legally available. Kratom is currently categorized as a new dietary ingredient that has not yet been approved by the US Food and Drug Administration. As such, the FDA requires safety data to be submitted before kratom can be approved as a dietary supplement. Several applications for kratom as a new dietary ingredient have been submitted but none have been approved.[58]

Kratom laws vary among US states. Some states have banned the sale of kratom, while other states regulate kratom, focusing on age restrictions, lab testing, labeling, and limits on 7-hydroxymitragynine due to its opioid-like potency.

There are other concerns about kratom, which include contaminants and adulterants, such as fungi, heavy metals, bacteria, and the addition of other potent related alkaloids such as 7-hydroxymitragynine, mitragynine pseudoindoxyl, and synthesis side products.[59–61] These contaminants and adulterants may lead to significant adverse effects and sometimes life-threatening toxicity.

The US FDA recognizes that current scientific and clinical knowledge about kratom is lacking. There are only a few published reports and clinical studies on kratom administration which have focused on safety and pharmacokinetics. Additional investigations into safety and potential therapeutic benefits need to be conducted.

In the United States, kratom has not been federally scheduled under the US Controlled Substances act. According to the US FDA, kratom has not been approved as a dietary supplement. There have been substantial public safety concerns and risk of adulteration. In the absence of federal regulation, some US states banned kratom products completely while other states imposed regulations such as "Kratom Consumer Protection Act" legislation.[62]

The regulatory approach for kratom in Canada is different. Kratom is not listed as a controlled substance but Health Canada has not approved kratom products for human consumption.[63]

With the growing evolution of kratom and interest as a potential therapeutic agent, there is a need for more clinical research to address questions related to the efficacy and long-term safety in humans, risk of dependence as well as drug interactions.[64]

Discussion

There has been a rapid growth in the variability of kratom products in recent years. Kratom has always existed in the form of native leaves; however, recent findings have demonstrated significant diversification in the commercial market, including concentrated extracts, isolates, edibles, capsules, and tea bag preparations.

This diversification may increase accessibility and consumer appeal, particularly among younger populations and individuals that are seeking psychoactive or self-medication effects. The various formulations which include concentrated products or isolated alkaloids are a major concern in the US as frequency and amount play major factors in the safety and toxicity of such products. Higher concentrated extracts and isolates are more likely to pose physiological dependence and toxicity risk.

The limited knowledge on newly emerging kratom formulations and especially concentrates and isolates raises concerns for adverse effects, dependence, and even fatalities in people who use kratom. Various products are labeled as "kratom"; however, consumers are not familiar with the product differences both in composition and effects which can lead to adverse outcomes. Therefore, it is essential that consumers have access to accurate labeling of kratom products as well as non-conflicting information that clearly states serving sizes or doses, risks for dependence and adverse effects, and composition of products. Healthcare providers should also be educated on kratom products which have potential drug interactions due to their inhibition of cytochrome p450 enzyme system, especially CYP 2D6 and 3A4.[65]

Mitragynine remains the main alkaloid and the most studied, with established pharmacological effects that are mediated through partial agonist activity at μ-opioid receptors, adrenergic, and serotonin receptors. Further research and in particular clinical studies regarding other kratom alkaloids is needed. Assumptions that most of the pharmacological effects of kratom are mainly due to mitragynine should be further assessed. Some of the structurally related isomers of mitragynine may prove to contribute to the complex pharmacology.

It is essential that consumers, healthcare professionals, and regulators are well educated about kratom and how to use the various formulations on the market. Consumers should inform their healthcare providers about any pre-existing

medical conditions and medications to best evaluate the potential for adverse effects and drug interactions that can emerge with concomitant kratom use.

State and federal monitoring are needed to establish and ensure adherence to good manufacturing practices and adequate quality control measures to ensure the absence of relevant and potentially harmful impurities or adulterants in kratom products.

There are potential therapeutic benefits of kratom; however, with the rise of more potent concentrated extracts and isolates there is an elevated risk for safety and toxicity. Further clinical studies and research are needed to evaluate the various new formulations on the market.

Conclusion

Kratom has emerged as a widely used herbal substance with increasing global attention due to its complex pharmacological profile and increasing commercial availability and potential for therapeutic benefits. Traditional kratom use remains prevalent in Southeast Asia for its cultural and medicinal use. Western commercial formulations have increased accessibility of potent kratom products among diverse populations, particularly individuals seeking pain relief, mood enhancement, prevention of withdrawal symptoms, or recreational effects.

There is evidence that suggests that highly concentrated kratom products can elevate the potential for tolerance, dependence, and potential toxicity in comparison with traditional preparations. Reports by the National Poison Data System in the US indicates an increase of approximately 1,200% in kratom-related exposure reports, with a marked surge in 2025.[66] Most toxicity cases are poly-substance exposures, involving substances of abuse and CNS active compounds linked to severe clinical outcomes including hospitalizations and kratom-involved deaths.

Diversification of kratom products and derivatives such as 7-hydroxymitragynine continue to be a public health concern. In order to differentiate native kratom leaf from other kratom products and derivatives, there has to be continuous monitoring, reporting, and documentation of the specific products involved, accurate labeling of products, and further research studies to ensure safety and pharmacology of kratom products and formulations in the market.

Disclosure

Dr Oliver Grundmann reports honoraria from Center for Forensic Science Research and Education; payments from law firms as an expert witness in legal cases involving kratom and other substances; board member and president of American College of Clinical Pharmacology, outside the submitted work. The authors report no other conflicts of interest in this work.

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