# A Pilot, Dose-Finding, Pharmacodynamic and Pharmacokinetic Study of Orally Administered Botanical Kratom

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**Background:** Kratom (*Mitragyna speciosa*) is a plant indigenous to Southeast Asia. This pilot study evaluated the pharmacodynamic (PD) effects, safety, and pharmacokinetics (PK) of kratom and several of its alkaloids.

**Methods:** Recreational polydrug users (8 participants/cohort; 6 active: 2 placebo, N = 40) completed the study. Participants had experience with opioids but were otherwise healthy. This study utilized a double-blind, between-subjects design where participants randomly received a single dose of placebo or kratom. The kratom used in the study had alkaloid levels representative of botanical kratom products (i.e., leaf) previously characterized in the literature and contained trace levels of 7-hydroxymitragynine (7-OH). The starting dose was 1 g and doses of 3, 8, 10, and 12 g were administered after safety reviews after each dose. After dosing, pupillometry and assessments of subjective effects were performed, and blood samples were collected. Safety assessments included adverse events (AE) monitoring, laboratory tests, vital signs, ECG assessments, physical examination findings, and assessment of suicidality.

**Results:** No deaths or serious adverse events (SAEs) occurred. Somnolence, vomiting, and nausea were the most common AEs reported. Kratom alkaloid concentrations showed generally orderly, dose-related effects. At doses ≥3 g, kratom produced pupillary constriction. Few dose-related effects were observed, although the 12 g dose of kratom produced increases on several subjective measures including ratings of "drug liking."

**Conclusions:** This study investigated the safety of single-sourced botanical kratom; the results may not be representative of other kratom-containing products. Kratom produced some opioid-like effects including pupillary constriction, and the 12 g dose produced effects commonly associated with drugs of abuse such as visual analog scale (VAS) ratings of drug liking, good effects, and high.

**Key Words:** kratom, abuse, pharmacokinetcs, pharmacodynamics

(*J Clin Psychopharmacol* 2026;00:000–000)

Kratom (*Mitragyna speciosa*) is a wetlands tree native to Southeast Asia including Thailand, Indonesia, and Malaysia.[1] Kratom has been used for centuries in a variety of sociocultural contexts including the treatment of opioid withdrawal, pain relief, and for mood-enhancing effects.[1–3] In the United States, kratom began increasing in popularity in the 1990s. According to the National Survey on Drug Use and Health, an estimated 1.7 million Americans aged 12 and older used kratom in 2021.[4] Characterizing kratom use is complicated by a heterogeneous product landscape that includes teas, tablets, extracts, and whole leaf products with varying routes of administration and alkaloid content. Much of the data regarding the use patterns of kratom in the United States is derived from survey-based studies. For example, Garcia-Romeu et al. found that most regular kratom users reported using 1 to 3 g (49%) or 4 to 6 g (33.4%) per consumption.[5] In other survey studies, the self-reported average consumption of kratom powder was 4 to 5 g per serving with a range of 2.6 to 7.5 g.[6,7] When quantifying mitragynine levels consumed through the use of kratom products, individuals self-reported consuming an average of 31.3 mg of mitragynine/serving, corresponding to 78.3 to 134.6 mg of mitragynine per day.[8]

As of November 2025, no drug products containing kratom or its components have been approved by the US Food and Drug Administration (FDA) and FDA has concluded that:

> *"…kratom is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury and, therefore, dietary supplements that are or contain kratom are adulterated under section 402(f)(1)(B) of the FD&C Act. Further, FDA has determined that kratom, when added to food, is an unsafe food additive within the meaning of section 409; food containing an unsafe food additive, such as kratom, is adulterated under section 402(a)(2)(C)(i). On the basis of these determinations by FDA, kratom is not lawfully marketed as a dietary supplement and cannot be lawfully added to conventional foods."*[9]

Received for publication September 29, 2025; accepted December 28, 2025.

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US Food and Drug Administration under contract 75F40121C00199.

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Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.psychopharmacology.com.



ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000002158

Despite the lack of regulatory oversight of kratom and kratom-related products, there has been substantial scientific interest in the pharmacology of kratom and its alkaloids. More than 40 alkaloids have been identified in kratom, the most abundant of which is mitragynine. Mitragynine accounts for ~66% of the total alkaloid content, and 4 additional alkaloids (speciociliatine, speciogynine, paynantheine, and corynantheidine) make up roughly 20% of the alkaloid content.[1,10] The minor alkaloids make up the remaining ~14% of alkaloid content of the leaf material and there are few data describing the pharmacological effects of these minor alkaloids.

Research efforts investigating kratom have focused primarily on its alkaloid constituents and mitragynine has been the subject of most of these studies given its abundance in the kratom in the tree. Mitragynine has affinity for, and binds to mu-opioid receptors.[11] Mitragynine also has affinity for a variety of receptor subtypes including adrenergic ($\alpha_{1a}$, $\alpha_{1b}$, $\alpha_{1d}$, $\alpha_{2a}$, $\alpha_{2b}$, and $\alpha_{2c}$), adenosine $A_{2A}$, dopamine $D_2$, and serotonin (5-$HT_{1A}$, 5-$HT_{2B}$, 5-$HT_{2C}$, and 5-$HT_7$) receptors.[12–14] The effects of mitragynine on mu-opioid receptors vary by the assay system utilized. For example, in vitro functional assays have characterized mitragynine as a full agonist,[15] partial agonist,[11,16] and as an antagonist.[17] In vivo assessments of antinociception using the hot plate test have shown that mitragynine functions as an agonist, producing a degree of antinociception similar to classic opioids such as morphine and oxycodone.[18,19] In contrast, mitragynine did not produce significant antinociception in hot plate tests utilizing rats.[17] Drug discrimination procedures have been used to examine the stimulus effects of mitragynine and model its subjective effects. In a drug discrimination study that trained rodents to discriminate mitragynine from vehicle, administration of morphine produced full substitution for the mitragynine cue.[20] In a second group of animals trained to discriminate morphine from vehicle, administration of mitragynine produced full substitution for the morphine stimulus cue (i.e., symmetrical generalization). Of note, the substitution of mitragynine for the morphine cue was dose-dependent: where the middle dose of mitragynine produced full generalization to the morphine cue but the low and highest doses examined did not.[20] Although the drug discrimination results from Harun and colleagues seem to be in keeping with mitragynine's mu-opioid receptor binding profile, disparate drug discrimination results have been reported. For example, in separate groups of rats trained to discriminate either mitragynine or morphine from saline, mitragynine failed to produce full substitution for the morphine stimulus cue, and morphine did not substitute for the stimulus effects of mitragynine.[17] Interestingly, a variety of other opioids did substitute for the mitragynine stimulus cue including fentanyl, nalbuphine, and buprenorphine.[17] The authors hypothesized that the incomplete substitution of mitragynine for morphine (and vice versa) may be due to rate-limiting effects, and that the stimulus effects of mitragynine are dose-related and may be mediated by more than mu-opioid agonist effects alone.

The rewarding properties of mitragynine have also been examined using conditioned place preference (CPP). In CPP studies with isolated mitragynine, rats demonstrated a place preference for mitragynine that was similar to stimulants and morphine, suggesting its rewarding properties.[21,22] A follow-up study using naloxone suggested that although opioid receptors mediated the acquisition of CPP, they were less involved in CPP expression after it was acquired.[23] In contrast, when the reinforcing effects of mitragynine were examined directly using self-administration procedures, mitragynine was not self-administered in rats previously trained to self-administer morphine.[24]

Although data characterizing the pharmacology of the minor alkaloids are sparse, 7-hydroxymitragynine (7-OH) has been the subject of numerous research efforts. 7-OH is typically reported to account for $< 0.05\%$ of dried kratom leaf mass, a substantially lower proportion than mitragynine.[25] 7-OH has been postulated to be a post-harvest artifact of kratom and is also formed as a metabolite of mitragynine in humans.[26] 7-OH has received considerable attention due to its greater affinity and activity at mu-opioid receptors relative to mitragynine and the other kratom alkaloids.[11,27] Importantly, 7-OH is self-administered in preclinical models, demonstrating its reinforcing effects and potential for abuse.[24]

Despite the extensive literature on kratom and its alkaloids using in vitro, in vivo, and epidemiological data to characterize its pharmacology and use patterns, prospective and properly controlled clinical studies are sparse. For example, Trakulsrichai and colleagues conducted a prospective study of the pharmacokinetics (PK) of kratom by administering kratom tea to regular kratom tea users. However, there was no placebo or positive control comparator, and subjective effects (i.e., abuse-related measures) were not assessed. In addition, the dose range of kratom was relatively limited and only 3 mitragynine equivalent doses were examined: 6.25, 9.96, and 11.5 mg.[28] Vicknasingam and colleagues examined the effects of kratom tea on pain tolerance using the cold pressor test. The authors found an increase in analgesia, though only a single dose of kratom tea was administered and mitragynine (1.6 mg/kg) was the only alkaloid measured in the tea.[29] Tanna et al.[30] also assessed the PK profile of a 2 g tea, whereas Huestis et al.[31] performed a double-blind, dose-escalation study of 0.5 to 4 g encapsulated dried leaf kratom powder administered orally to assess its PK profile. Other clinical assessments of kratom have allowed participants to self-administer their own kratom products in uncontrolled, outpatient settings without active or placebo comparators.[32–34] Given the dearth of rigorously controlled clinical studies of kratom, along with an absence of abuse-related outcome measures, the objective of this single ascending-dose study of botanical kratom was to generate pilot data on its behavioral effects and safety profile and to inform the design of a future human abuse potential (HAP) study.

## MATERIALS AND METHODS

### Study Design

This single-center, single-dose, randomized, adaptive, double-blind, placebo-controlled study consisted of 5 single ascending-dose cohorts. Dose levels could be adjusted to higher or lower doses following a review of the safety, tolerability, and pharmacodynamic (PD) data from previous cohorts by a Safety Review Committee (SRC). The SRC consisted of the principal investigator at the investigational site, the study manager, and personnel from FDA's scientific team. The study was conducted at Altasciences

company in Overland Park, Kansas. The study received ethical approval from an Institutional Review Board and was performed under an Investigational New Drug Application (IND).

## Kratom

The kratom used in the study was obtained from Sun Distribution, Super Organics. The kratom was powdered, raw leaf, and administered in 500 mg, size 00 capsules. To meet the chemistry, manufacturing, and controls (CMC) requirements for the IND, repeated stability testing was performed and the kratom met USP guidelines for heavy metals, microbial load, pesticides, mycotoxin, residual solvents, and moisture content. The kratom product was analyzed for alkaloidal content using a validated method UPLC-MS/MS as reported earlier,[35] and stability studies were performed at room temperature in a stability chamber (25°C and 60% RH) for 13 months. Kratom product was found stable (acceptable limit, 90% of initial content) and the alkaloid content seemed to be consistent with that reported in the published literature (Table 1).[8,36] For each cohort, matching placebo capsules containing 500 mg of microcrystalline cellulose were administered.

## Quantitative Analysis Using UPLC-MS/MS

Two separate bioanalytical methods were developed and validated for quantitative analysis of mitragynine and 7-hydroxymitragynine and speciogynine, speciociliatine, and paynantheine at Alta Sciences and University of Florida, respectively. In brief, mitragynine and 7-hydroxymitragynine were quantified using AB Sciex API5500 triple quadrupole mass spectrometer coupled with Shimadzu Nexera X2 ultra high-performance liquid chromatography system (UPLC-MS/MS) for a linearity range of 0.5 to 500 and 0.2 to 100 ng/mL, respectively. Analysis was conducted in multiple reaction monitoring (MRM) mode using precursor to product ion mass transitions of *m/z* 415.22 > 397.30, 399.23 > 238.10, 418.24 > 400.20, and 402.25 > 238.10, respectively, for 7-hydroxymitragynine, mitragynine, 7-hydroxymitragynine *d3*, and mitragynine *d3*, respectively. 7-hydroxymitragynine *d3* and mitragynine *d3* were used as an internal standard for 7-hydroxymitragynine and mitragynine, respectively. Chromatographic separation was achieved using a gradient flow (0.6 mL/min) of mobile phase consisting of methanol and water containing 0.5% formic acid and a Raptor biphenyl (100 ×2.1 mm, 2.7 μm) column. UPLC-MS/MS analysis of speciogynine, speciociliatine, and paynantheine was carried out using Waters Acquity Class I Plus UPLC coupled with a Waters Xevo TQ-S Micro triple quadrupole mass spectrometer for a linearity range of 1-250 ng/mL in human plasma. The chromatographic separation was achieved using Waters Acquity Premier CSH C18 (1.7 μm, 2.1×10 mm) with Vanguard fit guard column using the mobile phase consisting of aqueous ammonium acetate buffer, (2.5 mM, pH-3.5 ± 0.1) (A) – acetonitrile (B) with a gradient elution. The column and autosampler temperatures were kept at 55 and 4 °C, respectively. The mobile phase was delivered at a flow rate of 0.5 mL/min, and the injection volume was set to 2 μL. The source temperature was 150°C, Ion spray voltage was set at 500 V, desolvation temperature was 500 °C, desolvation gas flow was 900 L/h, and the cone gas flow was 50 L/h. The mass spectrometer was operated in positive ion mode and detection of the ions was performed in MRM mode, monitoring the transition of *m/z* 399.25 precursor ion $[M+H]^+$ to the *m/z* 174.16 product ion for speciogynine and speciociliatine (collision energy 32 V and cone voltage 60V), *m/z* 397.16 precursor ion $[M+H]^+$ to the *m/z* 174.16 product ion for paynantheine (collision energy 30 V and cone voltage 58 V), *m/z* 402.21 precursor ion $[M+H]^+$ to the *m/z* 177.06 product ion for internal standard (collision energy 30 V and cone voltage 26V) (mitragynine-*d3*). Both bioanalytical methods were validated for selectivity, specificity, accuracy, precision, calibration and range, carryover, matrix effect, dilution integrity, and stability following FDA/ICH M10 guidelines for bioanalytical method validation.

## Participants

A total of 40 healthy male and female, nondependent, recreational polydrug users with prior opioid experience were included in the study (8 subjects in each of the 5 cohorts). Recreational drug users were defined as those who had used opioid drugs for recreational purposes (i.e., for psychoactive effects) at least 10 times in the subject's lifetime and at least once in the last 12 weeks from screening. Inclusion criteria included a history of recreational use of 2 or more perception-altering (eg, lysergic acid diethylamide (LSD), kratom, cannabis, dronabinol, ketamine, phencyclidine, dextromethorphan, 3,4 methylenedioxymethamphetamine (MDMA), mescaline, psilocybin, tryptamine derivatives or ring-substituted amphetamines with perception-altering effects) or stimulant drugs (eg,

**TABLE 1.** Alkaloid Composition and Stability of Kratom Capsules (25°C/60% RH)

| | Timepoint (mo) | | | | | |
|---|---|---|---|---|---|---|
| **Alkaloid*** | **0** | **1** | **2** | **3** | **6** | **13** |
| Mitragynine | 5.22 ± 0.65 | 5.08 ± 0.35 | 4.90 ± 0.51 | 5.22 ± 0.46 | 5.07 ± 0.71 | 5.38 ± 0.32 |
| Speciogynine | 0.99 ± 0.12 | 0.96 ± 0.07 | 0.90 ± 0.10 | 0.97 ± 0.08 | 0.92 ± 0.13 | 0.94 ± 0.07 |
| Speciociliatine | 2.02 ± 0.24 | 1.98 ± 0.14 | 1.98 ± 0.21 | 1.94 ± 0.17 | 1.98 ± 0.26 | 1.82 ± 0.12 |
| Mitraciliatine | 0.29 ± 0.03 | 0.28 ± 0.02 | 0.29 ± 0.03 | 0.31 ± 0.02 | 0.29 ± 0.04 | 0.25 ± 0.02 |
| 7-hydroxymitragynine | 0.06 ± 0.01 | 0.06 ± 0.01 | 0.03 ± 0.01 | 0.03 ± 0.00 | BLLOQ | 0.04 ± 0.01 |
| Paynantheine | 1.34 ± 0.16 | 1.32 ± 0.09 | 1.26 ± 0.13 | 1.33 ± 0.12 | 1.28 ± 0.18 | 1.19 ± 0.08 |
| Corynantheidine | 0.14 ± 0.02 | 0.13 ± 0.01 | 0.13 ± 0.01 | 0.13 ± 0.01 | 0.13 ± 0.02 | 0.14 ± 0.01 |
| Corynoxine A | 0.05 ± 0.01 | 0.05 ± 0.01 | 0.05 ± 0.00 | 0.04 ± 0.00 | 0.04 ± 0.01 | 0.04 ± 0.00 |
| Corynoxine B | BLLOQ | BLLOQ | BLLOQ | BLLOQ | BLLOQ | 0.03 ± 0.00 |
| Mitraphylline | BLLOQ | BLLOQ | BLLOQ | BLLOQ | BLLOQ | BLLOQ |

*Alkaloids content(s) are expressed as the milligram (mg) amount per 500 mg capsule.
BLLOQ indicates below the lower limit of quantitation (1 ng/mL equivalent to 32 ng/capsule); RH, relative humidity.

cocaine, amphetamine, methamphetamine, methylphenidate, methcathinone, and other synthetic cathinones) on at least 5 occasions in the participant's lifetime. Polydrug recreational users with prior opioid experience were selected to ensure familiarity with a broad range of psychoactive drug effects. This population is considered appropriate and face-valid for evaluating the pharmacodynamic profile of escalating kratom doses, given its reported spectrum of activity ranging from stimulant-like effects at low doses to opioid-like sedation and dissociative/hallucinogenic effects at higher doses.[37–39] Experienced recreational polydrug users also represent the typical participant population enrolled in HAP studies, which this SAD study was designed to inform.[40] All participants provided written informed consent form (ICF) and agreed to use appropriate contraception methods (eg, abstinence, systemic contraceptives, intrauterine device, double-barrier method, etc.).

Exclusion criteria included: (1) Difficulty swallowing capsules; (2) females who were lactating or pregnant; (3) self-reported sensitivities to kratom; (4) significant history of disease including gastrointestinal, liver or kidney disease, cardiovascular, pulmonary, hematologic, neurological, psychiatric, gastrointestinal, endocrine, immunologic, ophthalmologic, or dermatologic disease; (5) smoking or a history of heavy smoking; (6) excessive caffeine intake; (7) other physiological diseases or abnormalities identified at screening, including ECG abnormalities and QT prolongation; and (8) additional criteria, including a history of substance use disorder and intake of kratom in the 14 days before study participation.

## Procedures

After successful screening, participants were confined to the clinical site from the day before drug administration until 48 hours after drug administration. Subjects were randomized 6:2 (active: placebo) to kratom or placebo in each cohort.

Kratom or placebo was administered under double-blind conditions. Study treatments were administered in the morning, 30 minutes after a standardized high-fat breakfast (fed state) after an overnight fast of at least 10 hours. This approach was chosen to increase tolerability, facilitate dose escalation, and mitigate nausea and vomiting previously reported under fasted conditions.[30] Capsules were administered with ~240 mL of water at room temperature. Given the large number and size of capsules required for certain cohorts (range of 2 to 24 size 00 capsules), an additional 240 mL of water was allowed if required. Time of dosing was set equal to the time when the first capsule was administered to the subject. The dosing procedure had to be completed within 5 minutes. Dosing procedures completed up to 2 minutes outside the allowed time window were not considered protocol deviations but were documented. Start and end times of dosing and the volume of water consumed were recorded. All capsules were swallowed whole and not chewed or broken.

## Safety

Safety assessments included adverse event (AE) monitoring, clinical laboratory tests, vital signs (blood pressure, pulse, respiratory rate, oxygen saturation, and body temperature), ECG assessments, physical examination findings, and assessment of suicidality using the Columbia-Suicide Severity Rating Scale. At the investigator's discretion, additional safety assessments could be performed as needed to ensure subject safety.

## Pharmacokinetic Assessments

Blood samples for PK measurements were collected predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, and 48 hours, post-dose. Samples were collected from an intravenous catheter or direct venipuncture, if necessary. The time of PK blood sample collection was calculated relative to the time of treatment administration. PK measurements of the study included plasma concentrations of mitragynine, 7-hydroxymitragynine, speciogynine, speciociliatine, and paynantheine using validated bioanalytical methods (see Supplemental Digital Content 1, http://links.lww.com/JCP/B19 and 2, http://links.lww.com/JCP/B24).

## Pharmacodynamic Assessments

Before completing computerized PD measures, all participants underwent a standardized training and practice session. Participants who seemed to have difficulty differentiating between bipolar and unipolar VAS (eg, making errors such as selecting a score of 50 to indicate the absence of a drug effect on a unipolar scale) or difficulty distinguishing between "at this moment" and "overall" measures received additional training focused on these distinctions.

Participants were monitored to ensure that PD assessments were completed appropriately. Reasonable attempts were made to rouse participants who fell asleep during testing. If a participant was unable to complete PD assessments in a timely manner before the next required procedure or timepoint due to an AE or other clinical concern, the PD assessment at that timepoint was aborted.

## Pupillometry

Data from a series of frames were used in the calculation of pupil size. Measurements were collected using a handheld electronic pupillometer (NeurOptics VIP-300 Pupillometer System, CA) under mesopic lighting conditions. For each participant, the same eye was used for all assessments when feasible. The pupillometry assessment was completed immediately before the administration of other PD measures at each prespecified timepoint.

## Visual Analog Scales (VAS)

All VAS were scored on a 0 to 100 scale and measured at predetermined time points. The VAS were structured as either bipolar or unipolar scales, depending on the subjective effect being measured. Bipolar scales asked about the neutrality, direction, and intensity of a subjective opinion, whereas unipolar scales only asked about the extremity or intensity of a subjective effect. When VAS were administered as bipolar scales, a neutral point equal to 50 was included in the scale [eg, drug liking, overall drug liking (ODL), take drug again (TDA), drowsiness/alertness VAS]. The neutral point reflected a state whereby a subject was experiencing neither negative nor positive effects (eg, neither dislike nor like the effects of the drug) and was labeled with an anchor, such as "neither like nor dislike." When VAS were administered as unipolar scales, anchors were presented using text such as "not at all" (score = 0) to "extremely" (score = 100; eg, good, bad, high, and any drug effects VAS). Unipolar scales did not include a neutral point but rather, a rating of "0" reflected the complete absence of a subjective effect, whereas a rating of "100"

reflected the maximum presence of a subjective effect (eg, no good effects = 0, extremely good effects = 100). Scales that referred specifically to drug (eg, drug liking, good drug effects, bad drug effects, and any drug effects VAS) were not administered at predose.

### Bowdle Visual Analog Scale

An adapted computerized version of the Bowdle VAS, consisting of 13 unipolar items, was administered to assess perceptual changes. Each item was scored from 0 ("not at all") to 100 ("extremely") with lower scores indicating fewer perceptual and psychedelic effects.

The individual items were:

1. My body or body parts seemed to change their shape or position (BODY)
2. My surroundings seemed to change in size, depth, or shape (SURROUNDINGS)
3. The passing of time was altered (TIME)
4. I had feelings of unreality (REALITY)
5. It was difficult to control my thoughts (THOUGHTS)
6. The intensity of colors changed (COLORS)
7. The intensity of sound changed (SOUND)
8. I heard voices or sounds that were not real (VOICES)
9. I had the idea that events, objects, or other people had particular meaning that was specific for me (MEANING)
10. I had suspicious ideas or the belief that others were against me (SUSPICIOUS)
11. I felt anxious (ANXIOUS)
12. I felt high (HIGH)
13. I felt drowsy (DROWSY)

Responses to items 1, 2, 3, 5, 6, and 7 were summed to produce a "subjective external perceptions" composite score. Response to items 4, 8, 9, 10, and 11 were summed to produce a "subjective internal perceptions" composite score. Items 12 and 13 were not included as they were administered as part of the individual VAS items. If a response to one of the items was missing, the associated composite score was not calculated.

### Drug Similarity VAS

Drug Similarity VAS items provided an estimate of how similar the test drug was to drug classes with which participants were familiar. On a unipolar scale ranging from "not at all similar" to "very similar," participants were asked to compare a drug they had taken previously to the test drug. A drug use history was completed during screening and used to create a subject-specific drug similarity measure. Drugs that a subject had not used often ( < 2 lifetime uses of a given drug), were not included in their questionnaire.

### Addiction Research Center Inventory (ARCI)

The Addiction Research Center Inventory (ARCI)[41–43] Morphine-Benzedrine Group (MBG), Amphetamine (A), Benzedrine Group (BG), Pentobarbital-Chlorpromazine-Alcohol Group (PCAG), and lysergic acid diethylamide (LSD) scales were administered alongside the basic VAS measures.

The 49-item ARCI was a shortened version (49 true-false items) compiled by Martin and colleagues from the original 550-item ARCI.[41–43] This version contained 5 scales, which measured the following effects: Euphoria—MBG scale; Stimulant effects—Amphetamine scale and BG scale; Dysphoria—LSD scale; and Sedation—PCAG scale. Subjects indicated their responses by selecting "false" or "true." One point was given for each response that agreed with the scoring direction on the scale (i.e., true items received a score of 1 if the answer was "true;" a score of 0 was given when the answer was opposite to the scoring direction).

The following scales were administered:

- Euphoria: Morphine-Benzedrine Group (MBG) scale
- Stimulant effects: Amphetamine (A) scale, Benzedrine Group (BG) scale
- Dysphoria: Lysergic acid diethylamide (LSD) scale
- Sedation: Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) scale

### Statistical Analyses

For measures collected within 24 hours, the peak responses [maximum ($E_{max}$) or minimum ($E_{min}$), as appropriate] were the endpoints. The primary pharmacodynamic endpoint was $E_{max}$ of drug liking VAS. Key secondary endpoints included Emax scores of high VAS, overall drug liking VAS, and take drug again VAS. Inferential statistics using the aforementioned peak responses were performed on the primary and key secondary endpoints. Because of the large number of endpoints and the large number of comparisons in the study, for controlling overall type I error rate only descriptive statistics were calculated for other endpoints.

ANOVA model was prespecified for the statistical analyses for the primary and key secondary endpoints. The 1-sided Dunnett test at 5% significance level was used for the comparisons between each dose of kratom and pooled placebo.[44] For the sensitivity analysis, Hodges-Lehmann estimator was used to estimate the difference between each dose of kratom and pooled placebo.[45,46] The 1-sided Mann-Whitney *U* test (or called Wilcoxon rank sum test)[47,48] at 5% significance level was used to test the null hypothesis that: "the observations produced by kratom and pooled placebo have the same distribution" versus the alternative hypothesis: "the distribution of observations produced by kratom is shifted to the right of that of pooled placebo." The Benjamin-Hochberg procedure[49] was used to adjust multiplicity for the comparisons between each dose of kratom and pooled placebo for each endpoint. As the dosing escalating study is exploratory in nature, the type I error rate adjustment was not performed for the multiplicity among endpoints.

## RESULTS

### Safety Analyses and Adverse Events

All 40 enrolled participants in the study were included in the safety analysis population. Overall, 18 of the 40 participants (45.0%) that received kratom or placebo experienced a total of 38 treatment-emergent adverse events (TEAEs) and 33 of the TEAEs (86.8%) were considered related to study drug (Table 2). The most commonly reported TEAEs were somnolence, vomiting, and nausea. Somnolence occurred in 1 of 6 participants (16.7%) receiving kratom 8 g, 3 of 6 (50.0%) receiving kratom 10 g, and 2 of 10 (20.0%) receiving placebo. Vomiting occurred in 2 of 6 participants (33.3%) in each of the kratom 8 g and 12 g cohorts, and in 1 of 6 (16.7%) in the kratom 10 g cohort. Nausea occurred in 2 of 6 participants (33.3%) receiving kratom 8 g, and in 1 of 6 (16.7%) in each of the kratom 10 g and 12 g cohorts. Nausea and vomiting

**TABLE 2.** Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and System Organ Class

| System Organ Class and MedDRA Preferred Term | Kratom 1 g (N = 6) 2 Capsules | Kratom 3 g (N = 6) 6 Capsules | Kratom 8 g (N = 6) 16 Capsules | Kratom 10 g (N = 6) 20 Capsules | Kratom 12 g (N = 6) 24 Capsules | Pooled Placebo (N = 10) | Overall (N = 40) |
|---|---|---|---|---|---|---|---|
| Subjects with at least one TEAE * | 1 (16.7) | 1 (16.7) | 5 (83.3) | 4 (66.7) | 3 (50.0) | 4 (40.0) | 18 (45.0) |
| Ear and labyrinth disorders | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 1 (2.5) |
| Tinnitus | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 1 (2.5) |
| Gastrointestinal disorders | 0 | 0 | 3 (50.0) | 2 (33.3) | 2 (33.3) | 0 | 7 (17.5) |
| Dry mouth | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 1 (2.5) |
| Nausea | 0 | 0 | 2 (33.3) | 1 (16.7) | 1 (16.7) | 0 | 4 (10.0) |
| Vomiting | 0 | 0 | 2 (33.3) | 1 (16.7) | 2 (33.3) | 0 | 5 (12.5) |
| General disorders and administration site conditions | 0 | 0 | 0 | 1 (16.7) | 1 (16.7) | 0 | 2 (5.0) |
| Chills | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 1 (2.5) |
| Feeling hot | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 1 (2.5) |
| Infections and infestations | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 1 (2.5) |
| Viral upper respiratory tract infection | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 1 (2.5) |
| Investigations | 0 | 0 | 0 | 0 | 0 | 1 (10.0) | 1 (2.5) |
| Blood pressure systolic increased | 0 | 0 | 0 | 0 | 0 | 1 (10.0) | 1 (2.5) |
| Musculoskeletal and connective tissue disorders | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 1 (2.5) |
| Neck pain | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 1 (2.5) |
| Nervous system disorders | 1 (16.7) | 0 | 2 (33.3) | 4 (66.7) | 1 (16.7) | 3 (30.0) | 11 (27.5) |
| Dizziness | 0 | 0 | 0 | 2 (33.3) | 0 | 0 | 2 (5.0) |
| Headache | 0 | 0 | 1 (16.7) | 0 | 1 (16.7) | 1 (10.0) | 3 (7.5) |
| Paresthesia | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 1 (2.5) |
| Presyncope | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (2.5) |
| Somnolence | 0 | 0 | 1 (16.7) | 3 (50.0) | 0 | 2 (20.0) | 6 (15.0) |
| Psychiatric disorders | 0 | 0 | 2 (33.3) | 2 (33.3) | 0 | 0 | 4 (10.0) |
| Anxiety | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 1 (2.5) |
| Euphoric mood | 0 | 0 | 1 (16.7) | 1 (16.7) | 0 | 0 | 2 (5.0) |
| Irritability | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (2.5) |
| Renal and urinary disorders | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (2.5) |
| Leukocyturia | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (2.5) |
| Skin and subcutaneous tissue disorders | 0 | 0 | 0 | 0 | 1 (16.7) | 1 (10.0) | 2 (5.0) |
| Hyperhidrosis | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 1 (2.5) |
| Pruritus | 0 | 0 | 0 | 0 | 0 | 1 (10.0) | 1 (2.5) |

Data are reported as n (%).

*Each TEAE was counted only once for each subject within each MedDRA SOC and PT.

MedDRA indicates Medical Dictionary for Regulatory Activities; N, number of subjects who received the specified treatment; n, number of subjects in a category; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

were not observed in the pooled placebo group. No serious adverse events or deaths were reported, and no participants discontinued the study due to TEAEs.

## Pupillometry

Mean (SE) pupil diameter over time at each dose level of kratom and placebo is illustrated in Figure S1 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20). Minimal fluctuations in pupil diameter were observed for placebo and kratom 1 g. In contrast, kratom doses of 3, 8, 10, and 12 g produced decreases in pupil diameter (i.e., constriction), with an apparent dose-related effect. Mean maximum pupil constriction over time was 0.9 mm for kratom 1 and 3 g, 2.2 mm for kratom 8 g, 1.9 mm for kratom 10 g, and 2.4 mm for kratom 12 g compared with 1.1 mm for placebo. Summary statistics for maximum pupil constriction are presented in Table 3.

Dunnett test[44] was used to test the difference in means between each dose of kratom and pooled placebo for maximum pupil constriction. The results showed that the means of maximum pupil constrictions produced by 8 and 12 g of kratom were significantly smaller (i.e., produced more pupil constriction) than that in the pooled placebo group ($P < 0.05$).

## Pharmacokinetic Results

All doses of kratom produced a measurable plasma concentrations of the targeted alkaloids.

### Mitragynine

Plasma concentration-time profiles for mitragynine are shown in Figure 1, and PK parameters are summarized in Table 4. After a single oral administration of kratom under fed conditions, mitragynine was absorbed into the systemic

**TABLE 3.** Summary Statistics for Maximum Pupil Constriction (mm)

| Parameter | Kratom 1 g (N = 6) | Kratom 3 g (N = 6) | Kratom 8 g (N = 6) | Kratom 10 g (N = 6) | Kratom 12 g (N = 6) | Pooled Placebo (N = 10) |
|---|---|---|---|---|---|---|
| Mean (SE) | −0.9 (0.2) | −0.9 (0.2) | −2.2 (0.3) | −1.9 (0.3) | −2.4 (0.4) | −1.1 (0.3) |
| Median | −0.7 | −0.8 | −2.2 | −1.7 | −2.3 | −0.8 |
| Min, max | −1.9, 0.3 | −1.5, −0.5 | −3.0, −1.2 | −3.1, −1.3 | −3.9, −1.1 | −2.6, 0 |

circulation with a median time to reach peak plasma concentration ($T_{max}$) ranging from 3.0 to 5.0 hours across cohorts 1 to 5. Mean observed peak plasma concentration ($C_{max}$) ranged from 41.7 to 378.5 ng/mL with increasing kratom doses from 1 to 12 g. The mean estimated area under concentration-time curve up to the last timepoint ($AUC_{0\text{-}T}$) ranged from 305.4 to 3271.2 h·ng/mL. An increase in mitragynine $C_{max}$, and $AUC_{0\text{-}T}$ was noted with an increased dose of kratom; however, dose-proportionality could not be concluded because of the limited number of subjects in parallel dosing cohorts.

## 7-Hydroxymitragynine

Concentration-time profiles for 7-hydroxymitragynine (7-OH) are shown in Figure 2, with PK parameters provided in Table 4. After a single oral administration of kratom under fed conditions, 7-OH produced a median $T_{max}$ ranging from 2.8 to 6.0 hours for cohorts 1 to 5. The mean observed $C_{max}$ ranged from 6.7 to 58.4 ng/mL with increasing kratom doses from 1 to 12 g. The mean estimated $AUC_{0\text{-}T}$ ranged from 53.5 to 574.3 h·ng/mL. An increase in 7-OH $C_{max}$, and $AUC_{0\text{-}T}$ was noted with an increased dose of kratom; however, dose-proportionality could not be concluded because of the limited number of subjects in parallel dose cohorts.

## Paynantheine

Plasma concentration-time profiles for paynantheine are shown in Figure S2 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20), with PK parameters provided in Table 4. Paynantheine produced a median $T_{max}$ ranging from 2.99 to 5.04 hours for cohorts 1 to 5. The mean observed $C_{max}$ ranged from 7.7 to 66.7 ng/mL with increasing kratom doses from 1 to 12 g. The mean $AUC_{0\text{-}T}$ estimate ranged from 47.0 to 727.6 h·ng/mL. An increase in paynantheine $C_{max}$, and $AUC_{0\text{-}T}$ was noted with increased dose of kratom; however, dose-proportionality could not be concluded because of the limited number of subjects in parallel dose cohorts.

## Speciogynine

Plasma concentration-time profiles for speciogynine are shown in Figure S3 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20), with PK parameters provided in Table 4. Speciogynine had a median $T_{max}$ ranging from 2.54 to 5.04 hours for cohorts 1 to 5. The mean observed $C_{max}$ ranged from 6.3 to 58.9 ng/mL after administration of kratom doses from 1 to 12 g. The mean estimated $AUC_{0\text{-}T}$ ranged from 53.4 to 819.2 h·ng/mL. An increase in speciogynine $C_{max}$, and $AUC_{0\text{-}T}$ was noted with increased doses of kratom; however, dose-proportionality

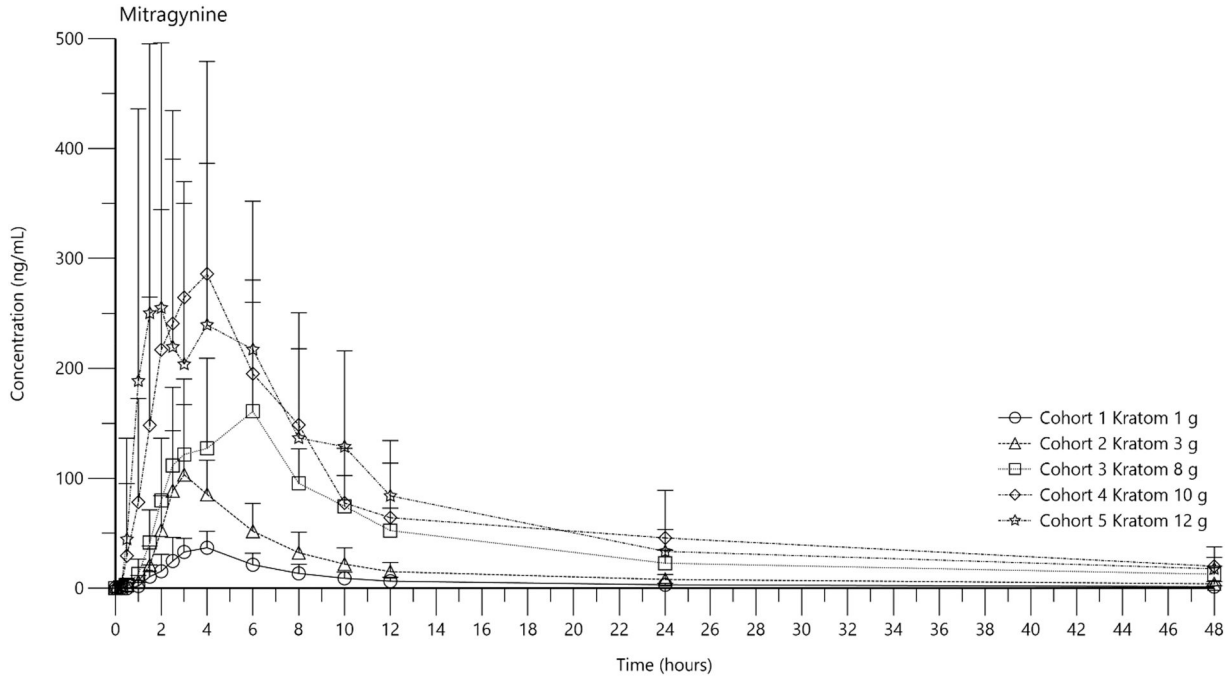


**FIGURE 1.** Plasma concentration-time profiles of mitragynine (Mean ± SD) by cohort in healthy participants (N = 6, each). The inset displays the 0 to 2 hours profile.

**TABLE 4.** Pharmacokinetic Parameters of Mitragynine and 5 Additional Alkaloids After a Single-Dose Oral Administration of Kratom to Healthy Participants

| Parameter* (Unit) | Cohort 1 (1 g) N = 6 | Cohort 2 (3 g) N = 6 | Cohort 3 (8 g) N = 6 | Cohort 4 (10 g) N = 6 | Cohort 5 (12 g) N = 6 |
|---|---|---|---|---|---|
| Mitragynine (mg) | 9.8-10.7 | 29.4-32.3 | 78.4-86.1 | 98.0-107.6 | 117.6-129.1 |
| $C_{max}$ (ng/mL) | 41.7 (35.4) | 118 (39.7) | 197.5 (44.7) | 318.1 (51.4) | 378.5 (48.9) |
| $T_{max}$ (h) | 4.0 (2.5-6.2) | 3.0 (2.5-4.0) | 5.0 (2.5-6.1) | 3.5 (2.5-4.0) | 2.0 (1.0-6.0) |
| $AUC_{0\text{-}T}$ (h·ng/mL) | 305.4 (37.9) | 784.8 (48.5) | 1942 (38.0) | 3254 (68.0) | 3271 (48.2) |
| $\lambda_Z$ (1/h) | 0.042 (21.5) | 0.038 (14.6) | 0.04 (24.5) | 0.034 (29.5) | 0.045 (22.1) |
| $T_{half}$ (h) | 17.28 (21.3) | 18.64 (15.2) | 17.47 (32.4) | 22.07 (30.2) | 15.9 (17.6) |
| 7-hydroxymitragynine (mg)† | 0-0.12 | 0-0.36 | 0-0.96 | 0-1.2 | 0-1.4 |
| $C_{max}$ (ng/mL) | 6.7 (32.4) | 17.8 (48.9) | 34.0 (32.9) | 48.4 (41.3) | 58.4 (38.9) |
| $T_{max}$ (h) | 4.0 (2.5-6.2) | 3.5 (3.0-4.0) | 6.0 (3.0-10.0) | 4.0 (3.0-4.0) | 2.8 (1.5-6.0) |
| $AUC_{0\text{-}T}$ (h·ng/mL) | 53.5 (40.4) | 132.9 (64.5) | 412.6 (37.2) | 459.1 (49.3) | 574.3 (33.9) |
| Metabolite:parent ratio (%) | 17.5 | 16.9 | 21.2 | 14.1 | 17.6 |
| Paynantheine (mg) | 2.38-2.68 | 7.14-8.04 | 19.04-21.44 | 23.8-26.8 | 28.56-32.16 |
| $C_{max}$ (ng/mL) | 7.7 (34.3) | 19.0 (26.5) | 29.7 (49.0) | 66.7 (54.8) | 65.8 (52.0) |
| $T_{max}$ (h) | 4.02 (2.5-6.18) | 2.99 (2.5-4.0) | 5.04 (3.0-6.14) | 3.0 (2.5-4.0) | 3.29 (1.5-6.01) |
| $AUC_{0\text{-}T}$ (h·ng/mL) | 47.0 (40.3) | 132.9 (33.1) | 320.2 (41.8) | 725.2 (62.4) | 727.6 (54.7) |
| $\lambda_Z$ (1/h) | 0.13 (44.4) | 0.077 (100.3) | 0.043 (26.2) | 0.041 (41.9) | 0.049 (21.1) |
| $T_{half}$ (h) | 6.33 (50.2) | 15.26 (60.2) | 16.86 (23.8) | 19.07 (35.0) | 14.7 (20.5) |
| Speciogynine (mg) | 1.8-1.98 | 5.4-5.94 | 14.4-15.84 | 18-19.8 | 21.6-23.76 |
| $C_{max}$ (ng/mL) | 6.3 (30.4) | 15.8 (27.2) | 23.2 (43.5) | 58.9 (60.3) | 55.5 (55.9) |
| $T_{max}$ (h) | 4.02 (2.5-6.18) | 3.0 (2.99-4.0) | 5.04 (3.0-10.02) | 4.0 (3.0-6.0) | 2.54 (1.5-6.01) |
| $AUC_{0\text{-}T}$ (h·ng/mL) | 53.4 (36.0) | 154 (28.6) | 341 (43.3) | 819.2 (63.7) | 790 (57.4) |
| $\lambda_Z$ (1/h) | 0.086 (69.6) | 0.052 (45.7) | 0.039 (16.9) | 0.038 (37.6) | 0.047 (19.4) |
| $T_{half}$ (h) | 11.06 (50.3) | 15.91 (42.8) | 18.09 (17.0) | 20.26 (34.9) | 15.20 (19.3) |
| Speciociliatine (mg) | 3.64-4.04 | 10.92-12.12 | 29.12-32.32 | 36.4-40.4 | 43.68-48.48 |
| $C_{max}$ (ng/mL) | 39.1 (30.0) | 106.6 (22.4) | 168.9 (40.3) | 388.1 (56.0) | 409.7 (47.3) |
| $T_{max}$ (h) | 4.02 (3.0-8.04) | 5.0 (3.0-9.99) | 8.07 (3.0-12.0) | 5.0 (4.0-8.0) | 5.06 (2.0-10.01) |
| $AUC_{0\text{-}T}$ (h·ng/mL) | 573.9 (49.7) | 1910.9 (24.9) | 3359.2 (37.4) | 7904.8 (60.6) | 7449.8 (49.6) |
| $\lambda_Z$ (1/h) | 0.072 (33.3) | 0.059 (24.8) | 0.056 (41.1) | 0.043 (18.7) | 0.062 (16.6) |
| $T_{half}$ (h) | 11.17 (52.6) | 12.55 (30.5) | 14.04 (35.1) | 16.39 (18.0) | 11.41 (14.8) |

*Doses are approximate based on measured alkaloid levels in capsules (Table 1).
†Some capsules were verified to have levels of 7-hydroxymitragynine below the limit of quantitation.
$\lambda_Z$ indicates elimination rate constant; $AUC_{0\text{-}T}$, area under concentration-time curve up to last timepoint; $C_{max}$, peak plasma concentration; $T_{half}$, elimination half-life; $T_{max}$, time to reach $C_{max}$.

could not be concluded because of the limited number of subjects in parallel dose cohorts.

### Speciociliatine

Plasma concentration-time profiles for speciociliatine are shown in Figure S4 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20), with PK parameters provided in Table 4. Median $T_{max}$ ranged from 4.02 to 8.07 hours for cohorts 1 to 5. Mean $C_{max}$ ranged from 39.1 to 409.7 ng/mL with increasing kratom doses from 1 to 12 g. The mean estimated $AUC_{0\text{-}T}$ ranged from 573.9 to 7904.8 h·ng/mL. An increase in speciociliatine $C_{max}$, and $AUC_{0\text{-}T}$ was noted with increased doses of kratom; however, dose-proportionality could not be concluded because of the limited number of subjects in parallel dose cohorts.

## Pharmacodynamic VAS Results

### Statistical Analysis on the Primary and Key Secondary Endpoints

In the tables and figures, K1, K3, K8, K10, K12, and P denote 1, 3, 8, 10, and 12 g doses of kratom, and pooled placebo, respectively. Table 5 summarizes the mean, SD, minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) rating for the primary and key secondary endpoints for all 6 treatments.

As shown in Table S1 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20), mean $E_{max}$ values produced by 8 and 12 g kratom had at least 10 points difference from the placebo group for the primary and all key secondary endpoints. A noticeable difference in median values between each dose of kratom and pooled placebo was found for the comparison between kratom 12 g and pooled placebo for all primary and key secondary measures except $E_{max}$ of Take Drug Again VAS. The median $TE_{max}$ for the primary endpoint was calculated and occurred ~1 hour post-dose for 12 g kratom. Figure S5 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20) shows the mean dose-response curves for these 4 endpoints. The mean dose responses produced by kratom 10 g for the primary and key secondary endpoints were all smaller than those produced by kratom 8 g. We plotted the heat maps for the individual time-course response profiles for 8, 10, and 12 g doses of kratom for the primary measure of drug liking VAS in Figure S6 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20).

Among the 6 participants who received kratom 8 g, one participant (ID 35) reported a drug liking VAS score of 100 at every timepoint, including the first assessment (i.e., 15 min after administration). Without including this subject, kratom 8 g would not show any meaningful effect on assessments of drug liking. Thus, it is possible the 12 g dose was the only dose to produce meaningful changes on subjective measures of drug effects. Figures S7A and S7B

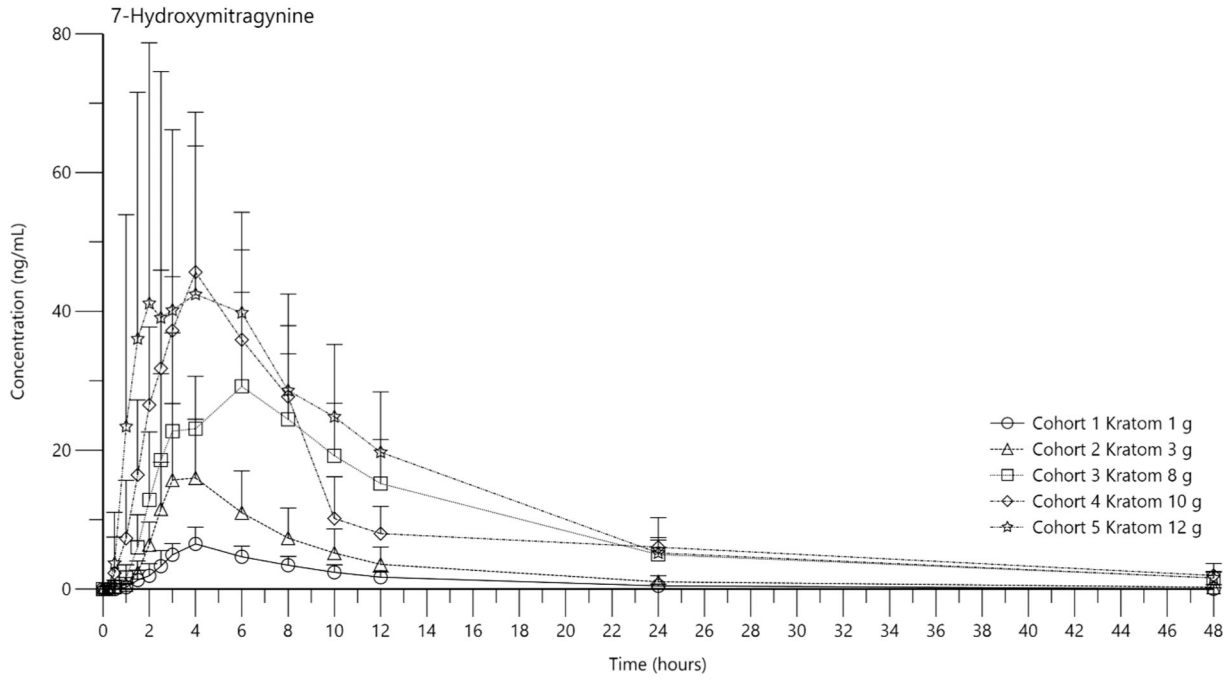


**FIGURE 2.** Plasma concentration-time profiles of 7-hydroxymitragynine (mean ± SD) by cohort in healthy participants (N = 6, each). The inset displays the 0-2 hours profile.

(Supplemental Digital Content 3, http://links.lww.com/JCP/B20) display the mean time-course profiles for drug liking VAS and High VAS.

In human abuse potential studies, the placebo range is typically considered to be between 40 and 60 for drug liking VAS. Figure S7A and S7B (Supplemental Digital Content 3, http://links.lww.com/JCP/B20) shows that the mean time-course profiles are bounded between 40 and 60 except the mean liking score of kratom 10 g that is below 40 eight hours post dose. For High VAS, the mean time-course profile for kratom 12 g is > 20 from 1.5 to 6 hours post dose. The peak mean response to kratom 12 g (33.7) occurred 6 hours post dose. As no data were collected between hours 6 and 8, it is possible, albeit unlikely, that the time to peak mean response occurs at hour 7.

Figure S8 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20) shows mean values with SDs for overall drug liking VAS and take drug again VAS 12 and 24 hours post dose for each treatment. Even though the means produced by pooled placebo were below 50, the means produced by kratom for these 2 endpoints were below, or close to 60.

## Inferential Statistics

An ANOVA model was used to test treatment differences for the primary and key secondary endpoints. To control for multiplicity, Dunnett's test was used to compare the means of kratom groups to pooled placebo. Significant treatment differences were demonstrated only for drug liking Emax and High Emax. The analysis results are presented in Table S1 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20).

The mean differences between kratom 12 g and pooled placebo were 18.5 and 45.9 for drug liking $E_{max}$ and High $E_{max}$, respectively. The analysis results show that the mean of kratom 12 g is significantly larger than that of pooled placebo at the significance level of 5% for these endpoints. The limitation of this inferential analysis is that the sample size for each treatment was very small. The assumptions of the ANOVA model were not met.

As a sensitivity analysis, Hodges-Lehmann estimator was used to estimate the difference between each dose of kratom and pooled placebo, the Wilcoxon Rank Sum test was conducted for each comparison, and Benjamini-Hochberg procedure was used for multiplicity adjustment. In the sensitivity analysis a significant result was only demonstrated in the comparison between kratom 12 g and pooled placebo for High Emax. However, clearly the difference in distributions between 8, 10, and 12 g doses of kratom and pooled placebo does not differ only in location. Therefore, the results from both the Dunnett test and Wilcoxon Rank Sum test should be interpreted with caution.

## Descriptive Statistics for other Endpoints

Descriptive statistics are provided for 8 VAS endpoints: Emax scores of any effects, bad effects, good effects, feeling drunk, bowdle external perceptions composite, bowdle internal perceptions composite, and $E_{min}$ scores of drowsiness/alertness, and relaxation/agitation, and 5 ARCI Emax endpoints: A, BG, LSD, MBG and PCAG, as well as Drug Similarity VAS. Table S2 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20) summarizes mean and SE for these endpoints produced by 8, 10, and 12 g doses of kratom and pooled placebo.

For kratom 12 g, VAS assessments of any effects, good effects, psychedelic effects (as measured through the Bowdle VAS), and bad effects were larger than those produced by 8 and 10 g doses of kratom and pooled placebo. Sedative effects (including PCAG) and LSD

**TABLE 5.** Summary Statistics for Primary and Key Secondary Pharmacodynamic Endpoints

| Endpoint: $E_{max}$ | TRT | N | Mean (SD) | Min | Q1 | Med | Q3 | Max |
|---|---|---|---|---|---|---|---|---|
| Drug liking VAS | P | 10 | 50.2 (0.4) | 50.0 | 50.0 | 50.0 | 50.3 | 51.0 |
| | K1 | 6 | 50.7 (1.6) | 50.0 | 50.0 | 50.0 | 51.0 | 54.0 |
| | K3 | 6 | 51.7 (4.1) | 50.0 | 50.0 | 50.0 | 52.5 | 60.0 |
| | K8 | 6 | 60.2 (20.0) | 50.0 | 50.0 | 50.0 | 70.8 | 100.0 |
| | K10 | 6 | 52.2 (2.4) | 50.0 | 50.0 | 51.5 | 54.5 | 56.0 |
| | K12 | 6 | 68.7 (22.6) | 50.0 | 50.0 | 60.0 | 95.0 | 98.0 |
| High VAS | P | 10 | 0.4 (1.0) | 0.0 | 0.0 | 0.0 | 0.3 | 3.0 |
| | K1 | 6 | 0.5 (1.2) | 0.0 | 0.0 | 0.0 | 0.8 | 3.0 |
| | K3 | 6 | 1.2 (2.9) | 0.0 | 0.0 | 0.0 | 1.8 | 7.0 |
| | K8 | 6 | 10.8 (12.1) | 0.0 | 0.0 | 9.0 | 21.3 | 28.0 |
| | K10 | 6 | 8.5 (13.0) | 0.0 | 0.0 | 3.5 | 16.0 | 34.0 |
| | K12 | 6 | 46.3 (34.6) | 0.0 | 22.5 | 37.0 | 83.5 | 94.0 |
| Overall drug liking VAS | P | 10 | 45.1 (15.5) | 1.0 | 50.0 | 50.0 | 50.0 | 50.0 |
| | K1 | 6 | 50.2 (0.4) | 50.0 | 50.0 | 50.0 | 50.3 | 51.0 |
| | K3 | 6 | 50.0 (0.0) | 50.0 | 50.0 | 50.0 | 50.0 | 50.0 |
| | K8 | 6 | 61.8 (20.5) | 50.0 | 50.0 | 50.0 | 78.3 | 100 |
| | K10 | 6 | 55.7 (32.4) | 2.0 | 37.3 | 55.0 | 79.8 | 100 |
| | K12 | 6 | 67.0 (19.5) | 50.0 | 50.0 | 63.0 | 85.0 | 94.0 |
| Take drug again VAS | P | 10 | 45.9 (16.4) | 0.0 | 49.8 | 50.0 | 50.0 | 60.0 |
| | K1 | 6 | 53.3 (7.7) | 50.0 | 50.0 | 50.0 | 55.5 | 69.0 |
| | K3 | 6 | 50.0 (0.0) | 50.0 | 50.0 | 50.0 | 50.0 | 50.0 |
| | K8 | 6 | 65.2 (19.7) | 50.0 | 50.0 | 59.0 | 79.8 | 100 |
| | K10 | 6 | 49.8 (42.0) | 0.0 | 0.8 | 56.0 | 89.5 | 100 |
| | K12 | 6 | 61.0 (21.0) | 42.0 | 48.0 | 50.0 | 83.0 | 95.0 |

$E_{max}$ indicates peak response expressed as the maximum response; K, kratom dose; Max, maximum; Med, median; Min, minimum; *P*, placebo; Q1, first quartile; Q3, third quartile; (1 = 1 g, 3 = 3 g, 8 = 8 g, 10 = 10 g, 12 = 12 g); TRT, treatment; VAS, visual analog scale.

(dysphoria) were also larger for kratom 12 g than those produced by other doses of kratom and pooled placebo.

The drug similarity unipolar VAS items provide an estimate of how similar the drug classes with which drug users have familiarity with are compared with the test drug. On a 100 mm scale ranging from "Not at all similar" to "Very similar," participants are asked to compare the drug they received that day to a drug they previously declared having familiarity/experience with taking.

Drugs that a participant has not personally experienced often enough to use as a standard of comparison ( < 2 lifetime uses of a given drug), are not included in the questionnaire. Most subjects had experience with benzodiazepines, nicotine, opioids, and THC. One subject in the kratom 10 g group and 3 subjects in the placebo group did not have experience with nicotine. One participant in the kratom 8 g group did not have experience with benzodiazepines.

From the summary statistics of Drug Similarity scores for benzos, caffeine, cocaine, ketamine, LSD, MDMA, methadone, nicotine, opioids, PCP, placebo, speed, Sudafed, and THC, Table 3 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20) displays summary statistics for participants choosing benzodiazepines, opioids, and THC which produced larger means compared with other choice of drugs by participants in 8, 10 and 12 g doses of kratom groups. Placebo ratings are also included. Although all participants in the pooled placebo group correctly recognized that placebo was not a benzodiazepine or opioid, ~75% of these participants assigned a Drug Similarity score of 100 to THC.

## DISCUSSION

This study was designed to evaluate the safety and tolerability, PK, and PD of single ascending oral doses of kratom in healthy, nondependent recreational polydrug users with opioid experience and to inform dose selection for a future human abuse potential study of kratom. Overall, using the specific botanical kratom sourced for the study and in a controlled clinical setting, kratom was generally well-tolerated in healthy subjects after oral doses of 1, 3, 8, 10, and 12 g. No serious adverse events (SAEs) or deaths occurred and no participants discontinued due to adverse events (AEs). The most frequently observed AEs were somnolence, nausea, and vomiting, which were observed at doses ≥8 g. The tolerability findings were likely attributable to kratom exposure rather than capsule burden, as placebo-treated participants who received an equivalent number of matched capsules did not exhibit similar AEs. However, the small sample size (n = 6 per dose) was insufficient to thoroughly characterize the safety profile of the kratom used in the study, and the study was not powered to capture rare or infrequent AEs.

Kratom doses of 8, 10, and 12 g produced measurable pupillary constriction relative to placebo. These data seem consistent with the reported agonist and partial agonist effects of kratom alkaloids (eg, mitragynine, speciociliatine, and 7-OH) on mu-opioid receptors. The magnitude of pupillary constriction produced by kratom was relatively mild, with a mean maximum constriction of −2.4 (0.38) mm at the 12 g dose. Although limited by cross-study comparisons, other investigations have reported larger reductions in pupil diameter after administration of classic opioids (eg, ≥ 3.0 mm after 40 mg oxycodone).[50,51] Although pupillary constriction may be considered a sign of mu-opioid receptor activation, many of the kratom alkaloids also exhibit affinity for mu-opioid receptors, as well as adrenergic, serotonergic, dopamine, and adenosine receptors, and their intrinsic efficacy at these receptor subtypes varies.[12–14,52,53] Moreover, the efficacy and activity of the alkaloids at these receptor subtypes can

vary, giving rise to the complex pharmacology of kratom that has led some authors to describe kratom as an "atypical opioid."[54]

Generally, kratom doses of 1 and 3 g were similar to placebo across subjective measures and did not show effects on VAS assessments of drug effects. Compared with placebo, increased at-the-moment drug liking and high, and overall drug liking, as well as a desire to take the drug again were observed for kratom 12 g. Kratom doses of 8 and 12 g showed increases in endorsements of positive subjective effects with 12 g showing the highest responses compared with placebo for most measures. However, across the primary and key secondary endpoints, only the 12 g dose showed a statistically and clinically significant difference compared with placebo for drug liking and High $E_{max}$. The 12 g dose was also associated with increased ratings of feeling drunk, and good drug effects compared with placebo. These ratings were generally ≥10 points above placebo, suggesting they were clinically significant and may be indicative of an abuse potential. Of interest, the 10 g dose did not show a similar degree of increase, despite being the intermediate dose of 8 and 12 g. Consistent with these findings, the 10 g dose showed a trend of pupillary constriction that was not as pronounced as the 8 or 12 g doses. Bad drug effects were highest for the 12 g dose compared with placebo. The mean $E_{max}$ of bad drug Effects produced by the 12 g dose was 25.5. Compared with placebo, the 8 and 12 g doses were associated with increased drowsiness and 8, 10, and 12 g doses were associated with increased relaxation. When examining psychedelic effects, only the 12 g dose showed elevated Bowdle VAS scores (mean External Perceptions 80.8; Internal Perceptions 67.3). Taken together with the AE profile (which did not show notable increases in the 10 g dose compared with 8 and 12 g), these data do not support the hypothesis that negative effects suppressed subjective responses at the 10 g dose. Rather, the apparent elevation in effects at 8 g seems to have been driven by a single participant (ID 001-035). This subject produced maximum ratings of drug liking at every timepoint, including the 15-minute post-dose time period where absorption of kratom is expected to have been minimal. This underscores the need for caution when interpreting data from small cohorts and highlights the potential value of qualification phases to identify and manage atypical response patterns in future studies.

The ARCI responses showed that the 12 g dose produced higher ratings of PCAG (sedatives) and LSD (dysphoria) compared with placebo. When assessed for similarity with known drugs of abuse, all doses of kratom were rated as being similar to THC (minimum similarity score = 82, maximum similarity score = 100). Kratom doses of 8, 10, and 12 g were also reported to produce effects similar to benzodiazepines and opioids. Irrespective of dose, kratom was not found to produce effects similar to drugs with stimulant or psychedelic-like properties including caffeine, cocaine, LSD, ecstasy, phencyclidine, or amphetamines.

Despite the limitations in the study due to few subjects in each dose cohort, plasma mitragynine, 7-hydroxymitragynine, paynantheine, speciogynine, and speciociliatine were measurable at every dose, and increased with dose as assessed by the extent of absorption after single doses of kratom from 1 to 12 g. Notable increases in the coefficient of variation were also observed with the administration of 10 g kratom for all compounds, with a general increase with increasing dose. Future studies may incorporate a larger sample size to decrease the variation observed in the PK data.

Peak plasma concentrations ($C_{max}$) of speciociliatine increased with dose as assessed by peak concentrations across the 1 to 12 g range. Plasma mitragynine, 7-hydroxmitragynine, paynantheine, and speciogynine increased in a slightly less than dose-proportional manner as assessed by peak concentration ($C_{max}$) after single doses of kratom from 1 to 12 g. The lack of dose-related increases in ($C_{max}$ and AUC) was seen in doses above 8 g, and continued with subsequent doses of 10 and 12 g under fed conditions. These data suggest there is saturation in absorption of these compounds. It is important to note that the number of capsules also increased with increasing doses. Given the large number of capsules necessary to administer the higher doses (eg, 20 and 24 size 00 capsules for the 10 and 12 g doses), it is possible the large volume of botanical plant matter inhibited or slowed absorption.

Median times to peak concentration for mitragynine, 7-hydroxymitragynine, paynantheine, speciogynine, and speciociliatine were all similar, with median $T_{max}$ values ranging from 2.00 to 8.07 hours. We note that the $T_{max}$ values generally did not occur before the 2-hour timepoint and did not coincide with peak effects on subjective measures. The interaction of PK and PD effects is complex. Although reviews have found that maximum ratings of dug liking generally occur no later than peak plasma concentrations $T_{max}$ or $C_{max}$ alone may not be predictive of abuse potential.[55] The average range of elimination for mitragynine and speciociliatine was similar between cohorts 1 to 5, with values ranging from 11.17 to 22.07 hours. There were only 2 additional blood sample measurements after 12 hours at 24 hours and the last sample at 48 hours. This sampling schedule is limited in accurately determining the elimination rates for all kratom alkaloids in this study. With these limitations considered the average range of elimination half-life values for 7-hydroxymitragynine, paynantheine and speciogynine were not similar between cohorts 1 to 5, with values ranging from 6.69 to 19.07 hours. Increases in average range of elimination generally correlated with increased dose. Notably, other studies of encapsulated dried kratom powder found differences in $T_{max}$ values, producing peak mitragynine concentrations 1 to 1.3 hours after administration and 7-OH $T_{max}$ values 1.2 to 1.8 hours after administration.[31] However, the dose range was lower (0.5 to 4 g) and participants received kratom under fasting conditions. The present study administered kratom in the fed state, after a high-fat meal and preclinical data have demonstrated food effects in the bioavailability of mitragynine.[56] Interestingly, when examining the $C_{max}$ values at identical (1 g) doses, broadly similar values were obtained, although there was substantial variability in our study due to the small sample size.[31]

An additional consideration when interpreting findings is the composition of kratom and the method of administration. Botanical formulations can vary greatly in the composition of the alkaloids that contribute to their pharmacological effects. Although mitragynine is the most abundant alkaloid isolated from kratom, minor alkaloids such as 7-hydroxymitragynine (which exhibits greater opioid potency than mitragynine and morphine)[37,38] and speciociliatine (which also has greater opioid activity than mitragynine)[13] may exert disproportionate influence on abuse-related and safety outcomes. The specific composition of the kratom used in this study contained ~5 mg of mitragynine per capsule (1% by weight) and low levels of 7-hydroxymitragynine (ranging from undetectable amounts to 0.07 mg/capsule). The kratom used in our study had alkaloid values similar to what has been reported in the literature;[8,10,36] however, it may be anticipated that different kratom

formulations with different alkaloid compositions or amounts may have variable pharmacological effects. The kratom sold in the United States is commonly in the form of dry plant material filled into capsules. In contrast, kratom use in Asian countries is commonly consumed as an herbal tea or chewed. Variability in composition, preparation, and administration may all affect bioavailability and exposure. In this study, dry plant material was filled into oral capsules, as would be commonly available in the United States. Future studies may examine various strains or the effects of isolated alkaloids in characterizing the safety, PK, and PD effects of kratom.

In summary, in the current study, orally administered botanical kratom was well-tolerated with the most commonly reported AEs observed at the highest doses (eg, 8-12 g) and classified as mild in severity (i.e., grade 2 or lower). Doses ≥ 8 g produced modest pharmacodynamic effects, including pupillary constriction, and all doses produced measurable plasma concentrations of key kratom alkaloids. Kratom alkaloid exposure was generally dose proportional and the time to maximum plasma concentrations ranged from 2 to 4 hours. The highest dose of kratom (12 g) was associated with increases in a variety of subjective effects measures associated with abuse potential, including statistically significant increases in drug liking and also on a positive measure of drug effects "high" relative to placebo. When subjects completed drug similarity measures, kratom effects were reported as resembling those of THC, and being somewhat similar to opioids and benzodiazepines.

The small sample size, between-subjects design, and absence of a qualification phase to reduce variability in response measures (eg, inappropriate responding on VAS measures) limit conclusions regarding the subjective effects and abuse potential of kratom. Appropriately powered studies are required to further characterize kratom's PD profile, safety, and its relative potential for abuse. Finally, although the botanical kratom used in the study was well-characterized, it is unknown how the kratom used in our study compares to the variety of kratom-related products available in the commercial marketplace. Although the kratom used in this study had an alkaloid profile consistent with botanical products reported in the literature, it seems to have a substantially different alkaloid composition relative to newly emergent "spiked" or enhanced kratom-related products in the commercial marketplace.[57–59] Further studies are necessary to more thoroughly characterize the abuse potential of botanical kratom and determine the effects of the various alkaloids on its pharmacological effects.

## AUTHOR DISCLOSURE INFORMATION

*C.M. has served as an expert witness in several kratom lawsuits. B.S. and D.K. are full-time employees of Altasciences. D.M. is a part-time consultant of Altasciences. The remaining authors declare no conflicts of interest.*

## DATA AVAILABILITY STATEMENT

*Funding Source: This study was funded by the US Food and Drug Administration under contract 75F40121C00199. Ethics Statement: Clinical studies with Kratom were conducted by Altasciences Inc. following approval of an institutional review board and written informed consent from participating subjects. Study procedures were carried out in accordance with the Declaration of Helsinki. Disclaimer: The opinions expressed in this article are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.*

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