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Safety and Tolerability of Single and Multiple Daily Oral Doses of Dried Kratom Leaf Powder in a Randomized Trial in Healthy Volunteers

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Background: Kratom use is rising, increasing the need for safety and tolerability studies of high-quality and well-characterized kratom products in humans. Kratom's risk–benefit ratio, recommended dose, treatment-emergent adverse events (TEAEs), abuse potential, and withdrawal require evaluation. Thus, the safety and tolerability of 4 escalating single and 15 daily dried kratom leaf powder doses in human volunteers were evaluated over 47 days in the largest controlled kratom-administration study to date.

Methods: A randomized, between-subject, double-blind, placebo-controlled, dose-escalation study of MitraLeaf kratom powder after single doses (SD), during 15 daily doses (multiple doses; MD), and a 23-day follow-up was conducted in 116 volunteers (49 MitraLeaf and 67 placebo). Twelve participants each received a SD of either 6.65, 13.3, 26.6, or 53.2 mg (n = 13) mitragynine in 500, 1000, 2000, or 4000 mg of MitraLeaf, respectively, with a 10-day follow-up. The same participants received 15 daily doses at the same concentration of SD mitragynine received, with a 27-day follow-up period. Inclusion criteria were nonsmoking healthy males and females who never used kratom or had not used kratom for ≥12 months, 18–55 years old, and BMI ≥18.5 and ≤29.9 kg/m^2. Participants were excluded if they had known CYP3A4, CYP2D6, or CYP1A2 genetic polymorphisms.

Results: No serious adverse events or deaths were reported. TEAEs after SD or MD generally increased as the dose increased. Dizziness, nausea, and feeling of relaxation were the most commonly reported TEAEs after SD, and headache, feeling hot, increased alanine aminotransferase level, and nausea were most common after MD.

Conclusions: This SD and first MD controlled study shows that *Mitragyna speciosa*–derived MitraLeaf kratom powder was safe and well tolerated at the dose ranges tested, with no evidence of meaningful abuse potential or withdrawal.

Key Words: kratom, mitragynine, safety, human administration, adverse events

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BACKGROUND

Mitragynine represents about 1%–2% w/w of kratom leaves of *Mitragyna speciosa*, and as the primary alkaloid, approximately 66% of the total alkaloid content of the leaves.[1] There are no US Food and Drug Administration (FDA)- or European Medicines Agency–approved uses for kratom or mitragynine; however, kratom users report taking kratom to improve their mood, increase energy levels, reduce fatigue, induce analgesia, and help manage their opioid use disorder.[2]

Kratom and mitragynine are not scheduled substances in the United States according to the Controlled Substances Act, although 6 US states currently ban kratom.[3] They are not included in the Single Convention on Narcotic Drugs of 1961 or the Convention on Psychotropic Substances of 1971. In 2021, the World Health Organization's Expert Committee on Drug Dependence completed a preliminary review of kratom and mitragynine and determined that they did not meet the criteria for potential inclusion as a banned substance.[4]

In 1967, Beckett and Morton[5] first reported 7-hydroxymitragynine (7-OH-mitragynine) as the major mitragynine metabolite (65.8%) after O-demethylation in rabbit liver microsomes. The primary CYP450 enzyme for mitragynine metabolism is the most abundant CYP3A4 that plays a predominant role in 7-OH-mitragynine formation, along with minor enzymes, CYP2D6 and CYP2C9.[6] Mitragynine was extensively metabolized in human liver microsomes primarily to O-demethylated and monooxidative metabolites. Zhang et al did not find detectable levels of 7-OH-mitragynine in fresh kratom leaves[7]; therefore, the metabolism of mitragynine via cytochrome P450 subtype 3A4 is the primary source of 7-OH-mitragynine in human plasma.

Mitragynine and 7-OH-mitragynine are partial agonists of the human μ-opioid receptor and competitive antagonists

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of κ- and δ-opioid receptors.[8] Compared with morphine, mitragynine in kratom extracts has a lower potency and affinity for μ-opioid receptors, is unable to induce comparable phosphorylation and GTPγS stimulation, and binds to κ- and δ-opioid and dopamine receptors.[9] Unlike full μ-opioid agonists such as morphine and fentanyl, mitragynine poorly activates the β-arrestin-2 pathway, which is implicated in many adverse effects of μ-opioid agonists, including respiratory depression and constipation.[10,11] Mitragynine and 7-OH-mitragynine are G-protein–based agonists of the μ-opioid receptor supporting early reports of the reduced respiratory depression of mitragynine compared with codeine,[12] and a more recent study demonstrating no significant respiratory depression in rats receiving up to 400 mg/kg oral mitragynine.[13]

The pharmacological profiles of mitragynine and its analog offer the possibility of analgesia with less respiratory depression; however, all compounds that attenuate nociception/pain are associated with reinforcing behavior and dependence.[2] In 2022, Henningfield et al[14] updated the assessment of kratom's abuse potential showing the relatively low abuse potential of kratom compared with morphine-like opioids, stimulants, and other abused drugs that have demonstrated robust rewarding effects across intravenous self-administration and intracranial self-stimulation models and conditioned place preference animal models. Humans consume kratom orally, rather than via inhalation or injection. Drugs that are inhaled or injected are delivered rapidly and in higher concentrations to the brain, thus increasing abuse potential. However, when high kratom doses are consumed frequently, physical dependence and withdrawal can occur, similar to other substances such as caffeine. Nevertheless, kratom withdrawal is much less intense than prototypical opioids such as fentanyl or oxycodone and is usually self-managed without clinical intervention.[15]

Mitragynine is also active at other receptors including α-adrenergic (α1A, α1B, α1D, α2A, α2B, and α2C), 5-HT_{2C} serotonin, 5-HT_7 serotonin, D2 dopamine, and A_{2A} adenosine receptors.[16–19] León et al[20] also reported potential mitragynine activity at the 5-HT_{1A} receptor. Thus, mitragynine's pharmacology is distinct from that of opioids, with only partial agonism at μ-opioid receptors and physiological and behavioral effects caused by its adrenergic, serotoninergic, dopaminergic, and adenosinergic activity.

Safety and tolerability studies with high-quality and well-characterized kratom products in humans are needed to assess the risk–benefit ratio and recommended doses and to evaluate behavioral and physical safety based on events including treatment-emergent adverse events (TEAEs), abuse potential, and withdrawal. To date, few in-human studies have evaluated the safety of kratom (*M. speciosa*).[21–23]

In an early kratom-administration study, 10 chronic (median use 1.75 years), regular (median kratom tea consumption 4 times/day), 1, 2, or 3 healthy kratom users received 6.25–11.5 mg of mitragynine in kratom tea for 7 days before receiving 6.25–23 mg of mitragynine doses orally.[21] No adverse events were reported. Median blood pressure and pulse increased from approximately 87 to 92 mm Hg and 75 to 77 bpm, respectively, peaking after 8 hours. Capillary blood glucose concentrations were normal throughout the study period, and all participants described tongue numbness after drinking the tea. No abnormal signs and symptoms were detected.

In another human controlled mitragynine-administration study, kratom tea was prepared by steeping 2 g of kratom containing 39 mg of mitragynine and no detectable 7-OH-mitragynine in hot water.[22] The tea was consumed within 10 minutes by 7 healthy participants (3 males, 4 females) with a history of kratom use. One female participant withdrew from the study due to nausea and vomiting 20 minutes after consuming the tea and was replaced by another female participant, who also withdrew 48 hours later after experiencing nausea, vomiting, and abnormal urine. Five participants completed the study, had no serious adverse events, and tolerated the kratom tea.

Tanna et al[23] later studied the drug interaction potential of kratom based on the effects of a single low dose of kratom tea (2 g) on the pharmacokinetics of the CYP3A4 probe substrate midazolam (2.5 mg) and CYP2D6 probe substrate dextromethorphan (30 mg). Twelve healthy adult participants drank kratom tea before oral administration of midazolam and dextromethorphan. Each gram of kratom leaves contained 19.5 mg of mitragynine resulting in a total dose of approximately 39 mg of mitragynine. Kratom had no effect on the area under the curve (AUC) and maximum plasma concentration (C_{max}) of dextromethorphan indicating that mitragynine/kratom did not affect CYP2D6 enzyme activity. However, the AUC and C_{max} of midazolam increased modestly while the half-life was unchanged, suggesting that kratom primarily inhibited intestinal CYP3A. Consuming kratom with drugs extensively metabolized by CYP3A could affect exposure to both drugs and elicit adverse events.

The current study was designed to assess the safety and tolerability of a well-characterized, raw, dried, *M. speciosa*–derived kratom leaf powder after single oral ascending doses (SD) and during and after 15 consecutive once-daily oral ascending doses (MD) in healthy adults under steady-state conditions.

MATERIALS AND METHODS

Study Design

A randomized, between-subject, double-blind, placebo-controlled, dose-escalation, single-site study of MitraLeaf (encapsulated dried kratom leaf powder, NP Pharma, Marietta, GA) was conducted for 10 days after administering SD and 15 MD and for 23 days of follow-up in healthy adults. There were 31 in-person clinical visits over 47 days; in the SD phase, dosing occurred on day 0, with data collection on days 1, 2, 3, 5, 7, and predose day 10, and in the MD phase, data were collected after the 15 MD on days 10–24 and on days 25–27, 29, 31, 34, 40, and 47. Intensive pharmacokinetic assessments were performed after each single oral MitraLeaf dose and on the last of 15 consecutive daily MitraLeaf doses. The study was conducted according to the Declaration of Helsinki and approved by the Advarra Institutional Review Board (protocol code 00048457 approved on 20 June 2022)

and Health Canada. Written informed consent was obtained from all study participants.

Study Population and Dosing

Inclusion and exclusion criteria are included in Table 1. Participant recruitment and stratification balanced the ratio of sex between active and placebo groups.

A dose of 1000 mg of MitraLeaf contained 13.3 mg of mitragynine and <0.01% 7-OH-mitragynine based on the Certificate of Analysis. Single doses of 6.65 (cohort 1), 13.3 (cohort 2), 26.6 (cohort 3), or 53.2 (cohort 4) mg of mitragynine in 500, 1000, 2000, or 4000 mg of MitraLeaf were administered in 1, 2, 4, or 8 capsules, respectively. Twelve participants each received the first, second, or third escalating doses, 13 received the highest dose, and 67 received placebo. Ten days after each single dose, the same participants received the same dose for 15 consecutive days.

Safety Analysis

Safety analysis was performed in all participants who received at least 1 single or multiple MitraLeaf doses. Safety measures included the number of participants with TEAEs and serious adverse events during dosing and for 23 days after the last dose was administered. TEAEs were monitored throughout the study. Safety laboratory parameters and assessment schedule are included in Table 2. Shifts in laboratory parameters, defined as a change from a value in the normal laboratory reference range to an abnormal value, were also recorded. A shift only indicated a change in the category, which was not necessarily clinically significant. Only shifts that were considered noteworthy (a participant had 3 or more shifts in a single parameter, or at least 3 participants had a single shift in the same parameter, or there was a clinically significant shift) were described. To minimize bias, the sponsor representative, PI, participants, and personnel interacting with participants were blinded to active or placebo interventional assignments.

Adverse Events

TEAEs are adverse events that occurred after the first dose, or medical conditions reported by the participant before the first dose but worsened during the study. TEAEs may or may not be related to the intervention. The frequency (number of events and number of participants) and incidence (percentage of participants) of each TEAE after each active dose or pooled placebo were reported if they occurred in more than 1 participant.

Abuse potential–related TEAEs were collected based on recommendations and definitions provided in the US FDA guidelines,[24] and definitions by Sellers and Romach,[25] and expanded to include all MedDRA-related terms. The definitions in Kosten and Baxter[26] were utilized to define withdrawal-related TEAE and further expanded to include all MedDRA preferred terms. Other abuse potential parameters including responses to the first question of the Drug Effect Questionnaire (DEQ) "Do you FEEL a drug effect right now?" recorded using a visual analog scale (VAS) and the Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS) administered before and

TABLE 1. Inclusion and Exclusion Criteria for Participants in the Study

Inclusion criteria
Males or females
18–55 years old
BMI ≥18.5 and ≤29.9 kg/m^2
Never used kratom or had not used kratom ≥12 mo
Agreement to use appropriate birth control method throughout the study
Females of childbearing potential testing negative on pregnancy tests and not breastfeeding and having no intention to get pregnant or breastfeed throughout the study
Exclusion criteria
Participant has allergies to the product
Known CYP3A4, CYP2D6, or CYP1A2 genetic polymorphism
Presence of gastrointestinal, hepatic, renal, cardiovascular, respiratory, autoimmune, endocrine, neurological, or active psychiatric diseases
Positive serology results for HIV (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV)
Participant has allergies to the product
History of cancer
Participant has allergies to the product
History of cancer
Acute illness within 2 weeks of the single kratom dose
Positive urine drug test
History of drug or alcohol abuse in last 12 mo
Leeds Dependence Questionnaire score ≥21
Consumption of ≥2 alcoholic beverages a day
Hepatic or renal dysfunction with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2×upper limit of normal (ULN) and serum creatinine or blood urea nitrogen (BUN) ≥1.5×ULN evaluated by the principal investigator (PI) for inclusion or exclusion
Blood donation or participation in another research study within past 4 wk
Medications that induced enzymes not permitted for 14 days or 7 half-lives of first dose; noninducers were permitted within 7 d

TABLE 2. Safety Parameters and Assessment Schedule

Safety Parameters	During Single Dosing Phase	During Multiple Dosing Phase
Comprehensive metabolic panel*	Baseline, days 0, 1, and 10	Days 25 and 47
Additional liver and kidney tests	Days 3 and 7	Days 11, 13, 15, 18, 22, 27, 34, and 40
Hematology panel	Baseline, days 0, 1, and 10	Days 25 and 47
Vital signs†	Baseline, days 0–7, and 10	Days 10–27, 29, 34, 40, and 47
RR‡ and capillary blood oxygen (SpO_2)	Baseline and before dosing on day 0	Before dosing days 10–24 and days 25–27
ECG	Baseline and before dosing on day 0	Day 24

*Comprehensive metabolic panel included liver and kidney tests.
†Vital signs included SBP, DBP, HR, and body temperature.
‡Respiratory rate.

after 15 daily kratom doses; a battery of cognitive tests with and without sleep deprivation are reported in a separate manuscript that focuses on kratom's abuse potential.

Data Analysis

The safety and tolerability of single oral ascending doses over 10 days and 15 daily repeated oral ascending doses of dried kratom leaf powder in healthy participants during steady-state conditions was summarized with the number and proportion of participants with at least 1 TEAE, clinical chemistry and hematological shift from baseline, vital signs, and ECG.

RESULTS

Participants

In total, 116 participants were enrolled in the study, 49 received active drug, and 67 received placebo. Participant demographics are shown in Table 3 for each SD and MD subcohort. Each cohort enrolled different participants, and participants completed both the SD and MD phases unless they were terminated early.

TEAE

There were no serious adverse events or deaths after administration of SD or MD dried kratom leaf powder or placebo. The percentages of participants receiving active kratom leaf who reported at least 1 TEAE after any SD, after any MD, and during the follow-up phase were 49.0%, 54.5%, and 25.0%, respectively. Of the participants receiving placebo, 41.8% reported at least 1 TEAE after SD, 50.0% after MD, and 20.0% during follow-up. Figures 1 and 2 shows the percentages of active and placebo participants reporting TEAEs at each SD and MD phase and during follow-up. Not all TEAEs were suspected to be related to the intervention by the physician evaluating the participants.

The percentages of participants who received active kratom and reported descriptively more TEAEs during MD compared with SD generally increased as the MitraLeaf dose increased. TEAE severity after receiving active kratom was evaluated as mild in 90% of SD reports, 97.5% of MD reports, and 50% of follow-up reports. Among the TEAEs reported by participants who received placebo, 92.1% were mild. Figure 2 shows the severity (mild, moderate, or severe percentage) of all TEAEs after active or placebo MitraLeaf in

TABLE 3. Participant Demographics

	Cohort 1 6.65 mg 500 mg		Cohort 2 13.3 mg 1000 mg		Cohort 3 26.6 mg 2000 mg		Cohort 4 53.2 mg 4000 mg		Placebo	
Mitragynine MitraLeaf	**SD**	**MD**	**SD**	**MD**	**SD**	**MD**	**SD**	**MD**	**SD**	**MD**
# Participants	12	11	12	11	12	10	13	12	67	60
Sex	6 F	6 F	4 F	4 F	4 F	3 F	7 F	6 F	33 F	28 F
	6 M	5 M	8 M	7 M	8 M	7 M	6 M	6 M	34 M	32 M
Race										
AI	0	0	0	0	0	0	2	2	3	2
Asian	2	2	5	5	1	0	0	0	10	9
Black	0	0	0	0	4	3	1	1	12	10
Unknown	0	0	0	0	0	0	1	1	2	1
White	10	9	7	6	7	7	9	8	40	38
Ethnicity	2 H	2 H	1 H	1 H	0 H	0 H	3 H	3 H	6 H	4 H
	10 NH	9 NH	11 NH	10 NH	12 NH	10 NH	10 NH	9 NH	61 NH	56 H
Mean age (STD) yr	30.8 (9.3)	31.3 (9.5)	32.9 (9.4)	33.9 (9.2)	35.8 (11.4)	37.3 (12.1)	33.2 (9.6)	33.9 (9.7)	32.7 (9.9)	33.4 (10.0)
BMI kg/m^2	23.1 (2.7)	22.8 (2.6)	25.3 (2.6)	25.4 (2.7)	26.2 (3.4)	26.1 (3.7)	23.4 (2.9)	23.8 (2.8)	25.4 (2.7)	25.5 (2.7)

AI, American Indian or Alaskan Native; F, female; H, Hispanic; M, male; MD, multiple doses; NH, Non-Hispanic; SD, single dose.

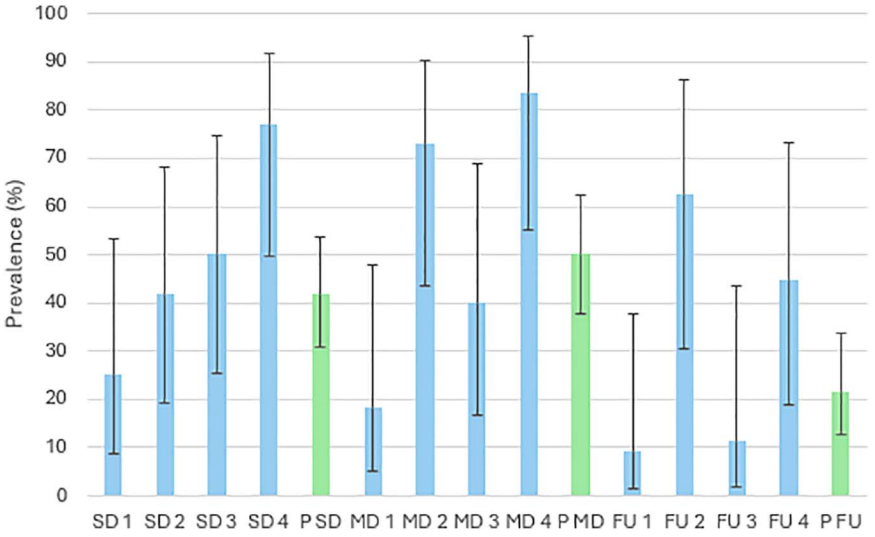

FIGURE 1. Percentage of participants reporting treatment-emergent adverse events (TEAEs) by cohort (dose) and study phase (SD, MD, and follow-up [FU]) after receiving active and placebo MitraLeaf (dried kratom leaf powder).

the SD, MD, and follow-up phases. With active MitraLeaf, 5 moderate and 1 severe TEAEs were reported after SD, 6 moderate and 1 severe TEAEs were reported after MD, and 5 moderate and 3 severe TEAEs were reported during follow-up. The severe TEAE during the SD phase was a severe vasovagal response during blood collection, whereas that during the MD phase was severe gastroenteritis after the administration of 13.3 mg of mitragynine (1000 mg of kratom). Both participants were withdrawn from the study by the PI, and the TEAE resolved without any sequelae. The 3 severe TEAEs during follow-up were not considered related to the active MitraLeaf administration. With placebo kratom, 8, 8, and 1 moderate TEAEs were reported in the SD, MD, and follow-up phases, respectively.

Nausea (8), dizziness (7), and headache (5) were the most common TEAEs reported across all active doses in the SD phase. After placebo SDs, the most common preferred terms for reported TEAEs were headache (8), dizziness (7), and somnolence (5). Table 4 includes the number and percentages of all TEAEs reported by more than 1 participant after receiving active MitraLeaf or placebo kratom (mitragynine) SDs.

Headache (11), feeling hot (6), nausea (5), somnolence (5), and increased ALT levels (5) were the most common preferred terms for TEAEs reported across all active MitraLeaf MDs, whereas headache (14), somnolence (5), and contusion (4) were the most common across all placebo kratom MDs. Table 5 includes all TEAEs reported by more than 1 participant after active or placebo kratom (mitragynine) MDs.

Six participants terminated the study early as the blinded investigator suspected the TEAEs to be related to the investigational product (IP). Two early terminations occurred in cohort 2. The first was initiated by the PI due to a moderate ALT increase of $<2\times$ULN, the a priori study criteria for stopping dosing, of 45 U/L on day 6 after the single dose to 83 U/L after the second and 98 U/L after the fourth multiple daily doses. The fifth multiple daily kratom dose was not administered, and the participant was early terminated from the study. The other early termination in cohort 2 was due to a severe TEAE of gastroenteritis after the ninth multiple daily doses. There were 3 early terminations in cohort 3, with only 1 suspected to be related to the IP. This

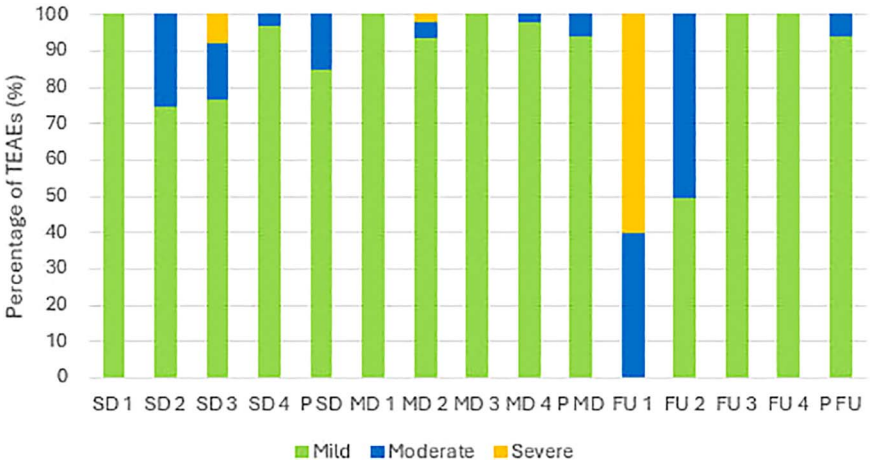

FIGURE 2. Mild, moderate, severe, and serious treatment-emergent adverse events (TEAEs) by dose and study phase (SD, MD, and follow-up [FU]) after receiving active and placebo MitraLeaf (dried kratom leaf powder). Three severe TEAEs in cohort 1 follow-up phase were considered not related to administration of the MitraLeaf (treatment intervention).

TABLE 4. Numbers and Percentages of Treatment-Emergent Adverse Events Reported by More Than One Participant After Receiving Single Doses of Active or Placebo MitraLeaf (Dried Kratom Leaf Powder) by Organ System

Single Dose	Reported Incidence by Kratom [Mitragynine] mg Dose, n				
Kratom mg Mitragynine [mg]	500 [6.65]	1000 [13.3]	2000 [26.6]	4000 [53.2]	Placebo
Total Number of Participants	n = 12	n = 12	n = 12	n = 13	n = 67
Number of participants who reported the events n (%)	2 (16.7)	5 (41.7)	5 (41.7)	10 (76.9)	19 (28.4)
Number of participants who reported nervous system–related events	0 (0.0)	3 (25.0)	3 (25.0)	8 (61.5)	17 (25.4)
Headache	0 (0.0)	1 (8.3)	0 (0.0)	4 (30.8)	8 (11.9)
Syncope	0 (0.0)	1 (8.3)	1 (8.3)	0 (0.0)	1 (1.5)
Dizziness	0 (0.0)	1 (8.3)	1 (8.3)	5 (38.5)	7 (10.4)
Somnolence	0 (0.0)	0 (0.0)	1 (8.3)	3 (23.1)	5 (7.5)
Presyncope	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (1.5)
Blood and lymphatic-related events	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Leukopenia	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Gastrointestinal events	1 (8.3)	1 (8.3)	2 (16.7)	4 (30.8)	3 (4.5)
Nausea	1 (8.3)	1 (8.3)	2 (16.7)	4 (30.8)	2 (3.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	2 (15.4)	0 (0.0)
Upper abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.0)
General disorders	0 (0.0)	2 (16.7)	2 (16.7)	5 (38.5)	4 (6.0)
Feeling relaxed	0 (0.0)	1 (8.3)	1 (8.3)	2 (15.4)	1 (1.5)
Feeling abnormal	0 (0.0)	1 (8.3)	1 (8.3)	0 (0.0)	1 (1.5)
Feeling drunk	0 (0.0)	0 (0.0)	0 (0.0)	2 (15.4)	0 (0.0)
Feeling hot	0 (0.0)	0 (0.0)	0 (0.0)	2 (15.4)	0 (0.0)
Increased energy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.0)
Psychiatric events	0 (0.0)	2 (16.7)	1 (8.3)	2 (15.4)	1 (1.5)
Hypervigilance	0 (0.0)	1 (8.3)	0 (0.0)	1 (7.7)	0 (0.0)
Euphoric mood	0 (0.0)	1 (8.3)	1 (8.3)	1 (7.7)	1 (1.5)
Injury, poisoning, and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.5)
Contusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.5)

participant voluntarily withdrew from the study due to multiple TEAEs on day 1 SD. Less than an hour after the first dose, the participant experienced vasovagal syncope for 1 minute, which coincided with an episode of "seizure-like activity" that fully resolved without behaviors such as disorientation or confusion. The PI reported no evidence of epileptic seizure, and due to its brief duration, no EEG evidence of seizure was obtained. This was the only report of "seizure-like activity" in any of the 49 participants receiving active drug; furthermore, vasovagal syncope is an event that may be misdiagnosed as seizure.[27,28] Dizziness and nausea were also reported by the participant, and they were withdrawn from the study.

Among 4 early terminations in cohort 4, 3 were due to suspected TEAEs. Two were withdrawn due to elevated ALT and AST during the MD phase, which resolved after cessation of the IP. One participant voluntarily withdrew after completing day 1 MD and reporting headache, feeling hot, feeling drunk, dizziness, nausea, and vomiting. All participants recovered from all TEAEs at the end of the study except 1 with a mild TEAE of uterine hemorrhage suspected to be related to the IP. Uterine TEAEs related to kratom or mitragynine have not been reported in the literature.

After receiving the lowest mitragynine dose (6.65 mg; across the SD, MD, and follow-up phases), 5 of 12 participants experienced 12 TEAEs; 7 TEAEs (58.3%) were mild, 2 (16.7%) moderate, and 3 (25.0%) severe. Five TEAEs were not suspected to be related to the IP, namely 2 moderate tremors and 3 severe events (1 severe presyncope and 2 severe syncope) in 1 participant receiving the lowest mitragynine dose; these events were associated with blood collection during follow-up. Seven adverse events were suspected to be TEAE-related events, with no TEAE reported in more than 1 participant in the SD, MD, or follow-up phase. One participant voluntarily withdrew early because of an adverse event before the first dose involving bruising at the catheter site. The remaining participants completed the study.

After receiving the 13.3 mg of mitragynine dose, 10 of 12 participants reported 63 TEAEs, of which 55 (87.3%) were mild, 7 (11.1%) moderate, and 1 (1.6%) severe. Eight TEAEs were not suspected to be related to the IP, including 5 mild and 3 moderate adverse events; 55 TEAEs were suspected to be related to the IP. No TEAE was reported in more than 1 participant in the SD or follow-up phase, but in the MD, headache (3) and feeling abnormal (2) were reported by a greater percentage of participants in the active group than in the pooled placebo group. A single participant in cohort 2 reported diarrhea in the follow-up phase.

Seven of 12 participants reported 39 TEAEs after receiving 26.6 mg of mitragynine; 36 (92.3%) were mild, 2 (5.1%) moderate, and 1 (2.6%) severe. Five TEAEs were not suspected to be related to the IP, including 4 mild and 1

TABLE 5. Numbers and Percentages of Participants Reporting Treatment-Emergent Adverse Events After Receiving 15 Daily Doses of Active or Placebo MitraLeaf (Dried Kratom Leaf Powder) by Organ System

	Reported Incidence by Treatment Group n				
Kratom mg Mitragynine [mg]	**500 [6.65] n = 11**	**1000 [13.3] n = 11**	**2000 [26.6] n = 10**	**4000 [53.2] n = 12**	**Placebo n = 60**
Number of participants reporting the events n (%)	2 (18.2)	7 (63.6)	4 (40.0)	10 (83.3)	25 (41.7)
General disorders	1 (9.1)	3 (27.3)	1 (10.0)	7 (58.3)	6 (10.0)
Fatigue	1 (9.1)	1 (9.1)	0 (0.0)	1 (8.3)	1 (1.7)
Feeling relaxed	0 (0.0)	1 (9.1)	0 (0.0)	1 (8.3)	2 (3.3)
Feeling abnormal	0 (0.0)	2 (18.2)	0 (0.0)	2 (16.7)	3 (5.0)
Feeling hot	0 (0.0)	0 (0.0)	1 (10.0)	5 (41.7)	0 (0.0)
Feeling drunk	0 (0.0)	0 (0.0)	0 (0.0)	4 (33.3)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (1.7)
Gastrointestinal disorders	2 (18.2)	1 (9.1)	2 (20.0)	8 (66.7)	6 (10.0)
Dry mouth	1 (9.1)	0 (0.0)	0 (0.0)	1 (8.3)	1 (1.7)
Abdominal pain	1 (9.1)	0 (0.0)	0 (0.0)	1 (8.3)	2 (3.3)
Upper abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)
Constipation	0 (0.0)	1 (9.1)	1 (10.0)	2 (16.7)	0 (0.0)
Diarrhea	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	2 (3.3)
Nausea	0 (0.0)	0 (0.0)	2 (20.0)	3 (25.0)	3 (5.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)
Infrequent bowel movements	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)
Psychiatric disorders	0 (0.0)	1 (9.1)	0 (0.0)	2 (16.7)	4 (6.7)
Hypervigilance	0 (0.0)	1 (9.1)	0 (0.0)	1 (8.3)	2 (3.3)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (1.7)
Insomnia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)
Nervous system disorders	0 (0.0)	4 (36.4)	3 (30.0)	8 (66.7)	18 (30.0)
Headache	0 (0.0)	3 (27.3)	2 (20.0)	6 (50.0)	14 (23.3)
Somnolence	0 (0.0)	1 (9.1)	0 (0.0)	4 (33.3)	5 (8.3)
Lethargy	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	1 (1.7)
Paresthesia	0 (0.0)	1 (9.1)	1 (10.0)	1 (8.3)	1 (1.7)
Dizziness	0 (0.0)	0 (0.0)	1 (10.0)	3 (25.0)	3 (5.0)
Discomfort in the head	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)
Injury, poisoning, and procedural complications	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	4 (6.7)
Contusion	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	4 (6.7)
Investigations	0 (0.0)	1 (9.1)	1 (10.0)	3 (25.0)	3 (5.0)
Increased ALT levels	0 (0.0)	1 (9.1)	1 (10.0)	3 (25.0)	1 (1.7)
Increased AST levels	0 (0.0)	0 (0.0)	1 (10.0)	2 (16.7)	0 (0.0)
Increased weight	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)
Skin- and tissue-related events	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	2 (3.3)
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	2 (3.3)
Metabolism- and nutrition-related events	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	1 (1.7)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	1 (1.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

moderate adverse event. Thirty-four TEAEs (including nausea) reported by more than 1 participant in the SD phase and by a greater percentage of participants in the active group than in the pooled placebo group were suspected to be IP-related events. During the MD phase, more than 1 participant and a greater percentage of participants in the active group reported headache and nausea than in the pooled placebo group. No TEAEs occurred in more than 1 participant in the follow-up phase.

After the highest mitragynine dose (53.2 mg), 11 of 13 participants had 246 TEAEs, of which 241 (98.0%) were mild, 5 (2.0%) were moderate, and none were severe. Seventeen TEAEs were not suspected to be IP-related events, including 16 mild and 1 moderate event. Of 229 suspected IP-related TEAEs, nausea, dizziness, feeling drunk, feeling hot, feeling relaxed, headache, somnolence (including 1 moderate event), and vomiting were reported in more than 1 participant in the active SD MitraLeaf group, and in a greater percentage of participants in the active group than in the pooled placebo group. During the MD phase, increased ALT, increased AST, constipation, decreased appetite, dizziness, feeling abnormal, feeling drunk, feeling hot, headache, infrequent bowel

movements, nausea, somnolence, and vomiting were reported by more than 1 participant and by a greater percentage of participants in the active MitraLeaf group than in the pooled placebo group. No TEAEs occurred in more than 1 participant during follow-up. All participants recovered from all TEAEs by the end of the study.

Hematology and Clinical Chemistry Shifts

No consistent trends in shifts from baseline to any postbaseline visit for hematology and clinical chemistry parameters were observed across cohorts after active MitraLeaf dosing, with no differences from pooled placebo. After receiving 13.3 mg of mitragynine, 1 participant was withdrawn from the study by the PI because of increased ALT that did not meet the a priori criteria of 2×ULN; the ALT concentration returned to normal after IP cessation. After receiving 53.2 mg of mitragynine, 2 participants who were withdrawn by the PI because of clinically significant elevations in ALT and AST, which resolved within 2 weeks after stopping the IP. There were no significant elevations in total bilirubin in any participant.

Vital Signs, RR, SpO_2, and ECG

The PI and medical monitor reported no clinically significant abnormal findings in BP, HR, RR, or SpO_2. Most abnormal findings were asymptotic and attributed to participants being nervous or in a hurry. After receiving 13.3 mg of mitragynine, 1 participant who completed the study reported a mild TEAE of palpitations on day 1 MD that resolved within 30 minutes; this participant did not have abnormal HR or BP at this time but experienced elevated but not clinically significant BP on day 12 MD, which returned to baseline at subsequent visits. Another participant in this cohort experienced low HR (not clinically significant), confirmed by an ECG indicating sinus bradycardia (not clinically significant) on day 1 SD at 12 hours postdose. This participant was withdrawn on day 14 MD before dosing due to a positive alcohol test.

One participant receiving placebo and none receiving active MitraLeaf had abnormal QTc. QTc >500 ms, the suggested level of concern for prolonged QTc, was not reported in any case. After receiving the highest MitraLeaf dose, 1 participant had large but not clinically significant variations in BP and HR on days 1 and 3 SD. This participant completed the study but reported anxiety in the clinic that may have impacted BP and HR. Another participant in this cohort who completed the study experienced significantly increased HR on day 1 SD at 55 minutes postdose, representing a mild TEAE of tachycardia, which resolved within 20 minutes. ECG results on day 1 SD predose and day 1 of the follow-up phase at 12 hours postdose for this participant indicated sinus bradycardia that was not clinically significant. No specific changes in vital signs or increase in abnormal values were observed with increasing dose. There were no clinically significant findings or notable differences from pooled placebo for respiratory function and ECG after the administration of any active MitraLeaf dose.

Abuse Potential and Withdrawal

The number of participants who reported abuse potential–related TEAEs increased with increasing dose. Dizziness was the most common abuse potential–related TEAE in the SD phase, and feeling hot was the most common TEAE in the MD phase. Euphoric mood, the primary abuse potential–related TEAE, was reported in only 3 participants, 1 in each active cohort and in the placebo cohort. No participant reported euphoric mood after receiving active kratom in the MD phase, whereas 1 participant receiving the MD placebo reported euphoric mood. Only 1 withdrawal-related TEAE, that is, mild diarrhea, was reported during the follow-up phase by 1 participant receiving 13.3 mg of mitragynine.

Published results of a pharmacokinetic study involving the oral administration of single and 15 daily doses of 6.65, 13.3, 26.6, or 53.2 mg of mitragynine through 500–4000 mg dried kratom leaf powder to 12 healthy controls (n = 13 for the highest dose) are summarized as follows.[29] Median (range) mitragynine C_{max} were 12.1 (1.8–61.5), 29.0 (16.0–58.1), 57.4 (20.4–90.0), and 130 (34.2–204.0) ng/mL with median (range) T_{max} of 1.0–1.3 (0.8–5.0) h after the administration of single 6.65, 13.3, 26.6, or 53.2 mg of mitragynine doses, respectively. Median (range) mitragynine C_{max} were 16.2 (2.8–60.1), 35.1 (21.8–43.1), 73.0 (42.4–109.0), and 155.0 (64.3–215.0) ng/mL with median (range) mitragynine T_{max} of 1.0–1.7 (0.8–4.0) h after 15 daily 6.65, 13.3, 26.6, or 53.2 mg of mitragynine doses, respectively. Median (range) 7-OH-mitragynine C_{max} were 3.6 (1.5–8.6), 7.0 (4.8–7.8), 11.0 (4.3–16.0), and 21.7 (12.5–38.6), with median (range) T_{max} of 1.2–1.8 (0.8–5.0) h after the same single oral mitragynine doses. Median (range) 7-OH-mitragynine C_{max} were 3.3 (1.4–5.6), 5.6 (4.3–8.1), 12.0 (6.9–17.4), and 20.9 (13.3–31.7) ng/mL, with median (range) T_{max} of 1.3–2.0 (0.8–4.0) h after 15 daily 6.65, 13.3, 26.6, or 53.2 mg of mitragynine doses. Steady-state concentrations were reached in 8–9 and 7 days with mitragynine and 7-OH-mitragynine, respectively. The mean 7-OH-mitragynine/mitragynine concentration ratios were 0.20–0.31 after SD and 0.15–0.21 after MDs.

DISCUSSION

The novel *M. speciosa*–derived MitraLeaf kratom powder was well tolerated in the SD and MD ranges tested. No serious adverse events or deaths were reported. All 4 doses had a generally acceptable safety profile in vital signs, RR, SpO_2, and ECG. Across all cohorts, 6 participants were withdrawn early, either voluntarily or at the PI's discretion, because of TEAEs suspected to be related to the IP. The lack of reported QTc abnormalities between the active and placebo groups and of prolonged QTc suggests that mitragynine does not significantly affect QTc duration, an important safety factor.

TEAEs were generally mild, with a few moderate and 3 severe TEAEs, namely, syncope during blood collection and gastritis. No trend was observed in any vital sign assessment or for increases in abnormal values with increasing dose. The percentage of participants receiving active MitraLeaf reported more TEAEs as the dose increased in the SD and MD phases. The most common TEAEs in the SD and MD phases were

nausea, dizziness, and headache, with additional common TEAEs in the MD phase, including feeling hot, somnolence, and increased ALT. Taken together, the study findings are consistent with those of other studies and evaluations of kratom pharmacology and safety, which suggest that kratom intake at commonly consumed levels poses low acute-safety risks.[30]

This study was conducted in healthy, nonsmoking individuals who did not use kratom recently, with all kratom doses administered in the clinic and extensive collection of safety data throughout the study. Additional studies are needed to evaluate the safety and tolerability of well-characterized kratom powder products in clinical populations and chronic kratom users. This is the first controlled study of multiple kratom powder doses, but despite the 23-day monitoring period after administering 15 daily kratom doses, possible long-term effects might not have been detected. Potential conflicts of interest are clearly disclosed, including the study's funding by NP Pharma, and compensations given to all authors for study design input and/or data analysis and publication.

A few potential abuse–related TEAEs were observed in a greater percentage of participants in the active MitraLeaf versus placebo groups; however, the primary potential abuse–related TEAE of euphoric mood was reported in only 1 participant receiving active SD and in 1 participant receiving placebo. Euphoric mood was not reported by any participant in the MD phase.

Regarding the frequency of clinically significant shifts in clinical chemical values, no consistent pattern was observed in any of the formulations across the lower dose groups. Results from the highest MitraLeaf dose group indicated increased incidence of clinically significant increases in liver function enzymes (ALT and/or AST) compared with the lower dose groups; no participant receiving any active dose showed elevations of >3×ULN ALT, ALP, or AST levels with >2×ULN total bilirubin levels, as per the US FDA's guidelines for drug-induced liver injury (DILI) caused by prescribed drugs.[31] Monitoring of liver enzymes and total bilirubin levels is recommended in future clinical studies.

Kratom was implicated in acute liver injury (mostly cholestatic), organ dysfunction, toxicity, coma, seizures, and, in a rare case, acute liver failure resulting in the need for liver transplantation.[32,33] Case reports describe liver function abnormalities associated with kratom use[34–40]; however, as the terminology varies in these reports, it is unclear whether these abnormalities fall within the scope of sustained DILI or acute and transient elevations of liver enzymes. Moreover, the case studies do not fully characterize the kratom substance ingested, the concentrations of mitragynine and other alkaloids, analysis of the product for adulteration or the presence of contaminants, the dose consumed, and frequency of use. The issue of liver function abnormalities is closely examined in the present prospective study on the safety, tolerability, and pharmacokinetics of MitraLeaf. Due to the increased ALT and/or AST levels after the ingestion of the highest active MitraLeaf dose, all hepatic function data were carefully reviewed.

The liver panel comprised AST, ALT, ALP, g-glutamyltranspeptidase (GGT), and bilirubin (total, conjugated, direct, and unconjugated). Elevations in liver enzymes may accompany injuries of the liver and other tissue damage (ie, muscle degradation, biliary obstruction) and are also noted after alcohol consumption. Therefore, it is critical to rule out other causes of elevations in individual liver enzymes alone, as these cannot necessarily be attributed to DILI.

Hy's Law is an interpretation of Zimmerman's observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an indicator of a drug's potential to cause serious liver injury.[41] Thus, a concurrent finding of usually substantial aminotransferase elevation with bilirubin >2×ULN indicates a drug likely to cause severe DILI that is fatal or requiring transplantation. To date, the small number of Hy's Law cases identified in clinical trials of various drugs present modest signs of hepatocellular injury. As defined in the FDA's Guidance for Industry: Drug-Induced Liver Injury Premarketing Clinical Evaluation (2009),[42] 3 criteria must be met for cases to fully adhere to Hy's Law: (1) the drug causes hepatocellular injury indicated by an elevation of 3×ULN ALT or AST levels compared with placebo; (2) elevation in serum total bilirubin >2×ULN is also present for at least 1 trial participant showing elevations after product exposure; (3) no other reason explains increased levels of aminotransferases and total bilirubin, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or a drug capable of causing the observed injury.

Overall, there were no consistent trends across all cohorts, or shifts from baseline to any postbaseline visit for clinical chemistry parameters in participants who received active MitraLeaf. None of the cases met the criteria of Hy's law or the FDA Guidance for DILI. AST or ALT elevations were >3×ULN in 3 participants, >5×ULN in 3 participants, and >10×ULN in none of the participants receiving active MitraLeaf. Bilirubin elevations were not >2×ULN in any participant. No combination of liver enzymes >3×ULN and bilirubin >2×ULN and no cases of AST or ALT >3×ULN were observed in conjunction with elevated AST or ALT temporally associated with nausea, vomiting, anorexia, abdominal pain, or fatigue. Furthermore, several participants who received placebo also experienced elevated aminotransferase levels that were of unclear etiology. AST, ALT, and total bilirubin monitoring is recommended in future clinical studies.

There are few data from randomized, placebo-controlled studies that address the cardiovascular effects of kratom or mitragynine. Therefore, it is important to examine the cardiovascular effects observed in the present study. In all the active MitraLeaf groups (n = 49), 3 participants reported abnormal vital signs after receiving different MitraLeaf doses, all of which resolved, and they completed the study. The abnormalities resolved in 2 of the participants, who eventually completed the study, whereas 1 participant was withdrawn by the PI because of reasons unrelated to the abnormal findings. Three participants across all 67 placebo volunteers also reported abnormal vital signs. Individual plots of the HR, DBP, and SBP of each participant showed no clear change over time.

Evaluation of mitragynine and 7-OH-mitragynine concentrations in addition to the extensive data on TEAEs, vital signs, and hematological and clinical chemistry parameters adds to the safety profile of the dried kratom leaf powder at the administered doses of 6.65–53.2 mg of mitragynine. Increases in mitragynine and 7-OH-mitragynine concentrations were proportionate to the dose based on their C_{max} and slightly greater than dose-proportional based on the AUC.[5] Mitragynine T_{max} after single and multiple oral mitragynine doses ranged from 1.0 to 1.7 hours, with only slightly longer T_{max} for 7-OH-mitragynine (1.2–2.0 hours). Accumulation factors for mitragynine comparing C_{max} and AUC at steady state during MD with C_{max} and AUC after a SD were low to moderate ranging from 1.0 to 1.3 and 1.6–1.9, respectively. Corresponding ranges of 0.9–1.0 and 1.0–1.3 were observed for 7-OH-mitragine indicating no or low accumulation after multiple dosing. This study is the first to provide complete data on the more potent 7-OH-mitragynine metabolite concentrations and 7-OH-mitragynine to mitragynine ratios in humans. 7-OH-mitragynine concentrations were always higher after SD compared with multiple mitragynine doses, and the highest ratios were consistently observed after lower rather than higher SD or MD. These data also confirm the observed positive safety and tolerability profile across the administered mitragynine doses.

CONCLUSIONS

This novel single- and multiple-dose randomized, placebo-controlled, double-blind study shows that *M. speciosa*–derived MitraLeaf kratom powder was safe and well tolerated at the dose ranges tested, with no evidence of meaningful abuse potential or withdrawal.

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