Journal of Pain 26 (2025) 104726

Contents lists available at ScienceDirect

The Journal of Pain

journal homepage: www.jpain.org

Original Reports

Kratom (*Mitragyna speciosa*) use for self-management of pain: Insights from cross-sectional and ecological momentary assessment data

Chung Jung Mun, Ph.D [a,b], Leigh V. Panlilio, Ph.D [c], Kelly E. Dunn, Ph.D [b], Johannes Thrul, Ph.D [d,e,f], Christopher R. McCurdy, Ph.D, FAAPS [g], David H. Epstein, Ph.D [c], Kirsten E. Smith, Ph.D [b,*]

[a] *Edson College of Nursing and Health Innovation, Arizona State University, Phoenix, AZ, USA*
[b] *Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[c] *Real-World Assessment, Prediction, and Treatment Unit, National Institute on Drug Abuse Intramural Research Program, Baltimore, MD, USA*
[d] *Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA*
[e] *Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA*
[f] *Centre for Alcohol Policy Research, La Trobe University, Melbourne, Australia*
[g] *Department of Medicinal Chemistry, College of Pharmacy, University of Florida, Gainesville, FL, USA*

ARTICLE INFO

Keywords:
Kratom
Mitragyna speciosa
Pain
Analgesia
Ecological momentary assessment

ABSTRACT

Kratom (*Mitragyna speciosa*) is increasingly used in the US for self-management of pain, despite limited research on its efficacy and safety. To better understand how and why people use kratom for pain self-management, we analyzed baseline survey data (N = 395) and 15-day ecological momentary assessment (EMA) data (N = 357) from kratom consumers across the US. Although we recruited participants based on their kratom use, not on whether they used it for pain management, nearly half (49.1 %) met criteria for chronic pain, with many reporting substantial pain relief and high effectiveness of kratom in managing pain. A majority (69.2 %) reported difficulties in obtaining adequate pain treatment, and most indicated that these challenges impacted their decision to try kratom. Most participants did not report concerns about overuse or significant side effects. EMA data showed that, regardless of chronic-pain status, pain relief was the most frequently endorsed primary motivation for daily kratom use. There were no significant association between daily pain levels and kratom use frequency, and no difference in the daily kratom use between those with vs. without chronic pain. Recent kratom use was associated with lower current pain levels. Stronger subjective effects of kratom were associated with lower pain levels. This effect was significantly moderated by chronic-pain status: those with chronic pain showed a stronger link between subjective kratom effects and pain reduction. These findings underscore the urgent need for systematic, rigorous research on long-term implications, efficacy, and safety of kratom in pain management to guide informed clinical practices and regulatory policies.

Perspective: This study reveals that chronic pain is common among kratom consumers, who frequently use it for pain self-management and report significant relief, as shown by ecological momentary assessment. There is an urgent need for research into kratom's safety, efficacy, and mechanisms to guide clinical practice and inform policies.

Introduction

Kratom is derived from the leaves of *Mitragyna speciosa*, a tropical tree indigenous to and widely cultivated in Southeast Asia.[1] Traditionally, kratom leaves are chewed or brewed into tea, serving as a folk remedy for health conditions, including pain, fatigue, depression, and opioid use disorder.[2] Since the mid-2010s, kratom use in the United States (US) has substantially increased, garnering significant public and scientific attention.[3–5] Current estimates suggest that between 10 to 16 million US adults regularly use kratom.[6–8] This widespread use of various kratom products highlights the need for a deeper understanding of kratom's potential benefits and risks, particularly as the US Food and Drug Administration (FDA) has not approved any kratom product as a drug, new dietary ingredient, or food.[5]

* Correspondence to: 5510 Nathan Shock Drive, Baltimore, MD 21224, USA.
E-mail address: ksmit398@jh.edu (K.E. Smith).

https://doi.org/10.1016/j.jpain.2024.104726
Received 3 August 2024; Received in revised form 10 October 2024; Accepted 1 November 2024
Available online 4 November 2024

US-based online surveys have consistently found that a widespread motivation for kratom use is chronic pain self-management.[9–12] Some preliminary evidence for kratom's analgesic effects were found in one placebo-controlled study conducted in Malaysia which demonstrated that kratom significantly enhanced cold pain tolerance in 26 healthy adult males who regularly consumed kratom.[13] These findings from self-report and lab-based studies likely reflect the activity of multiple alkaloids in kratom, specifically kratom's major alkaloid, mitragynine, and minor alkaloids, speciogynine, paynantheine, and speciociliatine, which have been shown in pre-clinical models to contribute to pain relief through opioidergic, serotonergic, and adrenergic mechanisms.[3,14–17]

Despite these laboratory and survey findings on kratom and analgesia, there are few human studies exploring the relationship between kratom use and chronic pain. There is a lack of basic information about its use and effects, such as the characteristics of chronic pain that individuals who use kratom typically report and how previous pain management attempts influence decisions to try kratom. Understanding consumers' use patterns and their perceptions of kratom's analgesic effectiveness is also important. These insights are foundational for advancing more systematic evaluations of kratom's influence on chronic pain.

The present study is a secondary data analysis of the first ecological momentary assessment (EMA) study recently conducted among US kratom consumers.[18] In that study, distal motivations for kratom use were identified via baseline survey, and proximal motivations for use were identified using EMA (motivations were not mutually exclusive in either type of assessment). Analyses revealed participants consumed kratom to increase energy, focus, alertness and productivity; to improve mood; and, for approximately one-third of the sample, to serve as a long-term substitute for substances such as opioids and alcohol. Baseline and EMA reports also revealed that pain relief was one of the most frequently endorsed motivations for kratom consumption.

In the present study, we are further examining baseline cross-sectional data and EMA data that provided real-time insights into kratom use and its effects. In doing so, we aim to provide the most granular investigation into kratom use for pain self-management to date. Using the study's baseline survey data, we examined characteristics of chronic pain among kratom consumers, identified their motivations for using kratom for pain management, and assessed their perceptions of kratom's effectiveness and side effects, as well as their perceptions about their use. Through EMA data, we further investigated how often pain relief motivated participants' daily use of kratom, how kratom-use frequency differed between those with versus without chronic pain, and whether daily pain levels were associated with kratom use frequency. Additionally, we examined how momentary pain ratings related to time since last reported kratom use, and whether feeling less pain was related to the overall perceived effects of kratom.

Methods

Detailed descriptions of the study methods[19] and primary outcomes of the study, including proximal motivators, effects, and patterns of kratom use, and assessment of whether use frequency was associated with motivations, effects, past-year criteria for substance use disorder for kratom, or other substance use have been previously reported.[18] Here, we provide the first secondary data analysis of the parent study and focus on examining the association between kratom use and pain; only methods relevant to the current analyses are described below.

We report baseline cross-sectional data findings based on 395 participants who enrolled in the EMA study. For EMA data, we focus only on the 357 participants who completed the full 15 days of EMA. Details on how we derived these sample sizes are below. The study received approval from the institutional review board (IRB) at the National Institutes of Health (NIH). Given the study's minimal risk, participants provided consent online via an attestation following a virtual informed-consent procedure that included a consent quiz.

Patient and public involvement statement

Patients or the public were not involved in the conceptualization, design, conduct, or dissemination of this study, including the choice of outcome measures and participant recruitment.

Participants

We recruited adults who use kratom on a regular basis, defined as at least three times a week for a minimum of four weeks prior to screening. This approach was intended to include both long-term users and recent initiates, ensuring sufficient use events for assessment via EMA. The main inclusion criteria were: (1) being 18 years or older, (2) living in the US, (3) passing validity checks, (4) owning a smartphone, (5) being willing to complete all study activities, (6) being willing to submit a sample of their kratom product, (7) passing an online informed-consent quiz with at least 80 % correct answers, and (8) demonstrating proficiency in English. The main exclusion criteria were: (1) failing one or more data-validity checks on the online screener, (2) completing the screener on a device that could not be verified as being within the US, (3) being decisionally-impaired and unable to provide consent, or (4) being incarcerated or in a controlled environment.

Participant recruitment and enrollment

Recruitment strategies included engaging kratom stakeholders (e.g., vendors, the American Kratom Association, bloggers, and podcast hosts) to disseminate materials via social media, email listservs, websites, and word of mouth. Additional recruitment targeted 36 US cities (listed in online supplement Table S1), chosen for their diversity, the legal status of kratom, and a wide distribution of suburban and urban areas. Additional recruitment methods included social-media posts, electronic flyers to other researchers, and paper flyers. Recruitment and screening were conducted between July-November, 2022.

Initial screening was conducted using an online questionnaire to determine preliminary eligibility. Participants who failed one or more data-validity checks or did not meet inclusion criteria were automatically screened out and informed of their ineligibility. Candidates who were not automatically screened out were informed that they might be eligible and would be notified via email within two business days. Staff manually screened provisionally eligible candidates by verifying Internet protocol (IP) addresses to ensure participants were US-based and not using a virtual private network (VPN). They also reviewed responses to an open-text question about participants' interest in the study to evaluate English proficiency and gather additional information. IP addresses were also used to help ensure that a candidate had not completed the screener more than once. This combination of automatic and manual screening helped prevent bots or bad actors from gaining study admission.

Those who passed the screening were emailed an enrollment invitation, allowing them time to read the informed-consent document, ask questions, and complete the informed-consent quiz. If a respondent failed the quiz more than once, they were automatically excluded from enrolling. After providing consent, participants completed a baseline survey. Out of 1152 eligible individuals who received an invitation link, 395 successfully consented, enrolled, and completed the survey. Among those invited who did not enroll (n = 757), 64.2 % did not respond to the invitation link (n = 486), 27.3 % did not attempt or pass the consent quiz (n = 207), and 8.5 % passed the quiz but did not complete the survey (n = 64).

Ecological momentary assessment (EMA)

After participants completed the baseline survey, they were invited

to download the EMA study app, which was specifically programmed by MetricWire on a platform that has been used in several previously published studies.[20–23] A total of 98.2 % (n = 388) of enrolled participants downloaded the app, with 53.9 % (n = 209) using Android devices and 45.9 % (n = 178) using iPhones. Upon downloading the app and creating login credentials, participants received a step-by-step tutorial to optimize their device settings for the app, along with tips for success during the EMA phase. This tutorial included an introduction to the "Resources" tab of the app, which provided a user guide and a copy of the informed-consent document on demand. Participants then entered their typical sleep-wake times for each day of the week, which were used to schedule EMA questionnaires during waking hours.

To address scheduling challenges for participants with bedtimes after midnight, participants were asked during onboarding whether they typically went to bed before or after 11:59 p.m. for each day of the week and their typical sleep/wake times for each day. Unique daily triggers were created so that the app recognized specific "days" for random prompting that could extend past midnight, adjusting as needed. This also allowed customization of participants' wake times by day.

The sampling strategy for the EMA phase included several components. Participants logged each kratom-use event in an event-contingent entry, documenting the product, dose, and proximal motivations for taking kratom. The first two event-contingent entries each day generated prompts for follow-up entries, delivered randomly 15–180 min later, to assess short-term effects and additional use. Participants were also prompted at random twice per day during waking hours and asked to complete entries. Lastly, participants completed beginning-of-day entries to assess sleep, and end-of-day diary entries to assess overall kratom effects that day and report any unreported kratom use.

To reduce response fatigue and prevent participants from withholding kratom-use reports, follow-up prompts for event-contingent reports were only triggered a maximum of twice daily. Thus, participants could receive no more than four randomized prompts daily but could make unlimited event-contingent (kratom use) entries. The follow-up window was purposefully wide to account for expected variability in the timing of kratom effects (likely to be affected by product formulation, dose, self-administration pace, and pharmacokinetic differences). Participants could also report any missed kratom-use events (i.e., events not already included in another report) during random and follow-up prompts and the end-of-day diary, where they could specify missed entries into five different time bins over the 24-hour period.

Participants who missed more than one EMA questionnaire per day for three consecutive days, without contacting the study team or having verified or plausible technical difficulties, were unenrolled from the study (n = 38) and notified via email and app text message. Typically, these participants had a high percentage of missed prompts (over 50 %). This unenrollment policy was implemented to ensure the precision of the study's conclusions, as increased missing data would reduce the accuracy of the findings. A total of 90.4 % (n = 357) of participants completed all 15 EMA days.

Measures

Baseline survey measures

Chronic-pain characteristics

The long-form version of the Brief Pain Inventory (BPI)[24] was used to assess various chronic-pain characteristics, including pain severity, pain interference, the body area that hurt most, and subjective type of pain ("aching," "sharp," etc.). Pain severity was determined by averaging four items (current pain, worst pain, least pain, and average pain over the past 24 h) on an 11-point scale from 0 (No Pain) to 10 (Pain as Bad as You Can Imagine). Pain interference was based on the average of six domain items (i.e., general activity, mood, walking ability, relationships with others, sleep, and enjoyment of life), each rated on an 11-point scale from 0 (Does Not Interfere) to 10 (Completely Interferes). The original BPI pain interference includes seven domains; however, due to an oversight, we did not assess the "normal work" domain. Internal consistency for pain severity and pain interference in the current sample was good, with values of .89 and .91, respectively. To describe subjective qualities of pain, participants selected from among 15 adjectives in the BPI.

Difficulty in accessing pain treatment and its influence on kratom use

All participants, regardless of their chronic pain status, were asked about their difficulty in accessing adequate pain treatment and how this influenced their decision to use kratom, using items that we had previously developed in a survey study.[4] They responded on a 5-point Likert scale (1 = Extremely difficult, 5 = Extremely easy) for the item, "During your lifetime, how difficult has it generally been for you to get what you believe is adequate treatment for any acute or chronic pain issues?" Those who responded "Difficult" or "Extremely difficult" were asked, "Did this at all influence your decision to use kratom?" with response options of "Yes," "No," and "Unsure."

Perceived pain relief after using kratom

All participants, regardless of their chronic pain status, rated the extent to which kratom typically provided pain relief for them, using items developed for this study. One item asked if participants had experienced pain relief over weeks or months of regular kratom use, with response options of "Yes," "No," and "Unsure." Another item asked participants to rate the pain relief experienced within minutes and hours after using kratom on a Visual Analog Scale (VAS) from 0 (No effect) to 100 (Strong effect).

Perceived effectiveness of kratom for acute and chronic pain management

All participants, regardless of their chronic pain status, reported the effectiveness of kratom on acute and chronic pain, using items developed for this study. Effectiveness was rated on a VAS from 0 (Not effective at all) to 100 (Extremely effective) for: (1) "Typically, how effective was kratom for relieving short-term (acute) pain?" and (2) "Typically, how effective was kratom for self-treating long-term pain issues and symptoms (chronic pain)?"

Concerns about overuse, and side effects of kratom for pain management

Participants with chronic pain were asked, "Are you concerned that you take too much kratom for pain specifically?" and "Are you having problems with side effects from your kratom that you take for pain specifically?" with response options of "Yes," "No," or "Uncertain." These items were adapted from the BPI,[24] on which the original phrasings were "Are you concerned that you use too much pain medication?" and "Are you having problems with side effects from your pain medication?"

Need for stronger kratom and more information on its use for pain management

Participants with chronic pain were asked, "Do you feel you need a stronger type of kratom for pain?" and "Do you feel you need to receive further information about your kratom that you take for pain specifically?" with response options of "Yes," "No," or "Uncertain." These items were adapted from the BPI,[24] on which the original phrasings were "Do you feel you need a stronger type of pain medication?" and "Do you feel you need to receive further information about your pain medication?"

EMA measures

End-of-day assessments

Primary reason for kratom use today

In the end-of-day diary report, participants were asked, "What was the primary reason that motivated your kratom use today?" Response

options were: (1) Relieve pain, (2) Help me sleep, (3) Feel less depressed or sad, (4) Stop worrying, (5) Calm me down, (6) Relieve kratom withdrawal, (7) Relieve other drug withdrawal, (8) Stop kratom craving, (9) Stop other drug craving, (10) Escape boredom, (11) Increase energy, (12) Increase focus/alertness, (13) Increase productivity, (14) Improve mood, (15) Relax and unwind, (16) Feel good, (17) Feel high, (18) Enhance the effects of another drug, and (19) Other.

Random-prompt assessments

Kratom use since last report

Participants were asked "Have you used any kratom since the last time you reported use?" with the following response options: "Yes," "No," and "I hadn't stopped—I'm still in the middle of taking/sipping my kratom." Due to the negligible response rate for the "I hadn't stopped" option (1.8 %), we focused on the binary responses of Yes and No.

Current pain level

This was assessed using the 0–100 VAS pain intensity rating ("Are you in pain right now?"). Note that, in addition to using this variable for moment-level modeling, it was also aggregated by calculating the average current pain level across all random prompt assessments for each day to examine the daily association between pain levels and kratom use frequency.

Follow-up assessments after event-contingent reports

In the follow-ups that were randomly prompted 15–180 min after a kratom-use report (i.e., event-contingent report), participants were asked, among other things, to make the following two ratings.

Level of current effects of kratom

"How much do you feel the effects of kratom right now?" was rated on a VAS scale (0 = Not at all, 100 = I feel them at their peak).

Pain levels since last kratom use

"Have you been in pain since your last kratom use?" was rated on a VAS scale (0 = Completely pain-free, 100 = Severe pain).

Determination of sample size

Rather than using a conventional null-hypothesis significance testing (NHST)-centered power analysis, we followed biostatistical advice to "power for precision."[25] This approach emphasizes obtaining narrow confidence intervals for point estimates, which provides robust statistical power for hypothesis testing without relying on conjectures about the distribution of outcomes—a common challenge in EMA studies. In designing our study, we leveraged data from one of our prior EMA studies with similar goals and conducted simulations using the BRMS package in R.[26] These simulations assessed Bayesian credible intervals across sample sizes from 40 to 240 participants, helping us evaluate the precision of key measures such as daily event-contingent entries and subjective effects. Our simulations indicated that the credible intervals for point estimates became sufficiently narrow at a sample size of 120, with further narrowing observed at higher sample sizes. Given this, we were confident that our sample size of 357 EMA completers, each providing 15 days of EMA data, is sufficient to address the study's questions. This approach allows for robust testing without the limitations of traditional NHST power analysis in the context of EMA.

Data analysis plan

All analyses were conducted using R software version 4.1.1. The baseline data were analyzed descriptively and visualized using bar plots and histograms, with the *ggplot2* package employed for data visualization. For the baseline data, we summarized the characteristics of the study sample and key variables of interest using frequencies, percentages, means, and standard deviations (SDs).

For the EMA data, the analysis involved several steps. First, we examined EMA compliance rates by calculating the percentage of automated prompts answered out of the total prompts administered. These compliance rates are presented with 95 % confidence intervals (95 % CIs), calculated using nonparametric bootstrapping to ensure robustness. Next, each of the study measures was assessed descriptively. To examine the potential difference in daily kratom-use levels between participants with chronic pain and those without, we used an independent-samples t-test. To test associations between variables, we used mixed-effects modeling. Specifically, we analyzed how the last reported kratom use was associated with current pain severity and whether current levels of kratom effects were associated with pain severity. We further explored whether chronic-pain status (Yes vs. No) significantly moderated these associations by conducting additional analyses that included chronic-pain status as a moderator. The mixed-effects approach was chosen due to its ability to handle the nested structure of EMA data, where moments (entries) were nested within days, and days were nested within participants. The assumptions of mixed-effects models were examined visually. To accurately evaluate level-1 effects (i.e., moment-level within-person associations), all level-1 predictor variables were day-mean centered, which involved subtracting the day's mean from the original momentary ratings. The mixed-effects models included random intercepts to account for individual variability, as well as a set of fixed effects to examine the primary research questions. In investigating the association between daily pain levels and kratom use frequency, we employed a Poisson mixed-effects model, as the outcome variable (i.e., kratom use frequency) was a count. This approach is well-suited for modeling count data. The *lme4* package in R was used for implementing mixed-effects modeling.

Results

Participant characteristics

A total of 395 participants were enrolled, with a mean age of 38.1 years (SD = 11.2, range = 18–76); 42.3 % identified as female, and 2.8 % as gender nonbinary. Most identified as Non-Hispanic White (90.9 %). In terms of sexual orientation, 78.7 % identified as heterosexual, 10.4 % as bisexual, and the remainder as gay, lesbian, queer, asexual, or preferred not to say. Participants were generally well-educated, with 32.9 % having some college education and 19.0 % holding a Bachelor's degree. Employment status showed 56.5 % working full-time, 13.4 % part-time, with smaller percentages being unemployed, disabled, students, or retirees. Most participants had an annual income of $40,000 or below and had used kratom uninterrupted for more than one year. Additionally, 36.7 % of the participants considered themselves to currently be in recovery from problems with alcohol or other drugs. See Table 1 for participant characteristics. We have provided Supplementary Table S2, which details the breakdown of participants by state and county. Using the Beale code, each county was classified as either metro or non-metro. There were no statistically significant differences in any of these characteristics between EMA completers (n = 357) and EMA non-completers (n = 38).[18]

Findings from baseline survey

Characteristics of chronic pain

Our analysis revealed that 49.1 % of the sample met the criteria for chronic pain, defined as experiencing pain for at least three months. Average pain severity was moderate (4.1, SD = 1.9; range: 0–10), as was average pain interference (5.4, SD = 2.4; range: 0–10). Fig. 1a shows body parts most affected, with the pelvic area/hip/back region being the most common at 27.3 %, followed by the stomach (17.5 %), and neck

Table 1
Demographic characteristics of baseline survey completers and EMA completers.

	Baseline Survey Completers (n = 395)	EMA Completers (n = 357)
Age	38.1 (11.2)	38.0 (11.1)
Sex/gender		
Male	217 (54.9)	198 (55.5)
Female	167 (42.3)	149 (41.7)
Nonbinary	11 (2.8)	10 (2.8)
Race/ethnicity		
White/European	359 (90.9)	325 (91.0)
Hispanic/Latino	25 (6.3)	22 (6.2)
Native American/Pacific Islander	17 (4.3)	14 (3.9)
Black/African American	11 (2.8)	10 (2.8)
Biracial/Multiracial	18 (4.5)	17 (4.8)
Asian	12 (3.0)	9 (2.5)
Middle Eastern	5 (1.3)	5 (1.4)
Indian	1 (0.3)	1 (0.3)
Sexual Orientation		
Heterosexual	311 (78.7)	282 (79.0)
Gay/Lesbian	13 (3.3)	11 (3.1)
Bisexual	41 (10.4)	35 (9.8)
Asexual	5 (1.3)	5 (1.4)
Queer	8 (2.0)	8 (2.2)
Don't know	2 (0.5)	2 (0.6)
Prefer not to say	8 (2.0)	8 (2.2)
Other	7 (1.8)	6 (1.7)
Education		
Some college	130 (32.9)	118 (33.1)
Associates/Vocational Degree	81 (20.5)	71 (19.9)
Bachelor's Degree	75 (19.0)	67 (18.8)
High school/GED	61 (15.4)	57 (16.0)
Master's Degree	31 (7.9)	28 (7.8)
Ph.D., M.D., or J.D.	9 (2.6)	9 (2.6)
9–12th grade, but didn't finish high school	8 (2.0)	7 (2.0)
Primary employment status		
Working full-time	223 (56.5)	201 (56.3)
Working part-time	53 (13.4)	48 (13.5)
Disabled	44 (11.1)	43 (12.0)
Unemployed	46 (11.7)	41 (11.5)
Student	19 (4.8)	15 (4.2)
Retired	10 (2.5)	9 (2.5)
Annual income in USD		
$0 - $10,000	61 (15.4)	57 (16.0)
$10,001 - $40,000	167 (42.3)	151 (42.3)
$40,001 - $70,000	83 (21.0)	74 (20.7)
$70,001 - $100,000	44 (11.1)	37 (10.4)
$100,001 - $150,000	27 (6.8)	25 (7.0)
> $150,001 - $200,000	13 (3.3)	13 (3.6)
Longest period of uninterrupted kratom use since initiating use[a]		
1–3 months	14 (3.8)	12 (3.5)
3–6 months	14 (3.8)	12 (3.5)
6–12 months	59 (15.9)	50 (14.7)
1–2 years	69 (18.5)	64 (18.8)
2–5 years	144 (38.7)	137 (40.2)
> 5 years	72 (19.4)	66 (19.4)
Considers themselves to currently be in alcohol/drug recovery	145 (36.7)	135 (37.8)
How did you hear about the study?[a]		
Reddit	145 (36.7)	131 (36.7)
Facebook	88 (22.3)	77 (21.6)
The American Kratom Association	66 (16.7)	62 (17.4)
Friend or family	43 (10.9)	39 (10.9)
From an online retailer or vendor that sells kratom	22 (5.6)	20 (5.6)
Podcast	15 (3.8)	14 (3.9)
An online forum or private group	19 (4.8)	18 (5.0)
Twitter	10 (2.5)	9 (2.5)
A local kratom advocacy group	7 (1.8)	7 (2.0)
Instagram	8 (2.0)	6 (1.7)
From an in-person shop that sells kratom	6 (1.6)	5 (1.4)
From a NIDA research team member	4 (1.0)	3 (0.8)
I work in a kratom shop and I heard through customers or co-workers	2 (0.5)	2 (0.6)
Chronic pain status (yes)	194 (49.1)	175 (49.0)

[a] Choices are not mutually exclusive.

(16.0 %). Regarding types of pain (refer to Fig. 1b), "Aching" was the most reported at 85.6 %, followed by "Nagging" and "Throbbing," both at 55.2 %.

Difficulty in accessing pain treatment and its influence on kratom use

As shown in Fig. 2a, 69.2 % of participants reported that obtaining adequate treatment for their acute or chronic pain conditions was either "Difficult" or "Extremely Difficult." Among those who rated their difficulty as "Difficult" or "Extremely Difficult," a substantial majority (86.2 %) indicated that these challenges had influenced their decision to use kratom (see Fig. 2b).

Perceived pain relief after taking kratom

As shown in Fig. 3a, most participants (93.2 %) reported experiencing pain relief over weeks or months of regular kratom use. They typically rated the pain-relieving effect as strong (M = 80.3; range: 0–100), occurring within minutes to hours after consumption (see Fig. 3b).

Perceived effectiveness of kratom for pain management

As shown in Fig. 4a-b, participants reported overall high effectiveness of kratom in managing both acute pain (M = 80.8; range: 0–100) and chronic pain (M = 83.9; range: 0–100).

Concerns about overuse, and side effects of kratom for pain management

As shown in Fig. 5a, most participants with chronic pain (83.7 %) expressed no concerns about overusing kratom for pain management. Additionally, 88.0 % reported currently experiencing (at the time of the baseline questionnaire) no side effects from their kratom use for pain management (see Fig. 5b). However, 7.1 % *were* concerned about overuse, and 7.6 % had problematic side effects.

Need for stronger kratom and more information on its use for pain management

As shown in Fig. 5c, most (60.9 %) participants felt no need for a stronger type of kratom for managing pain, but a substantial number (23.9 %) did. Furthermore, 73.4 % indicated that they did not require additional information about the kratom they use for pain management, but 19.6 % did (see Fig. 5d).

Findings from EMA data

EMA compliance

Compliance rates were high for end-of-day entries (91.36 % [95 % CI: 89.71, 92.93]), and slightly lower for random-prompt entries (85.61 % [95 % CI: 83.88, 87.22]) and post-kratom follow-up entries (84.44 % [95 % CI: 82.76, 86.05]). There were no significant differences in compliance rates by age, participation in kratom advocacy, sex/gender, or smartphone device.

Primary reasons for kratom use today

Participants were asked about their daily primary motivation for kratom use in the end-of-day diary. On 33.6 % of days, the primary reason was "relieving pain." In participants who met baseline criteria for chronic pain, this percentage was higher: 58.4 % of days. In both the full sample and the sample limited to chronic pain, "relieving pain" was the most frequently endorsed primary motivation for kratom use.

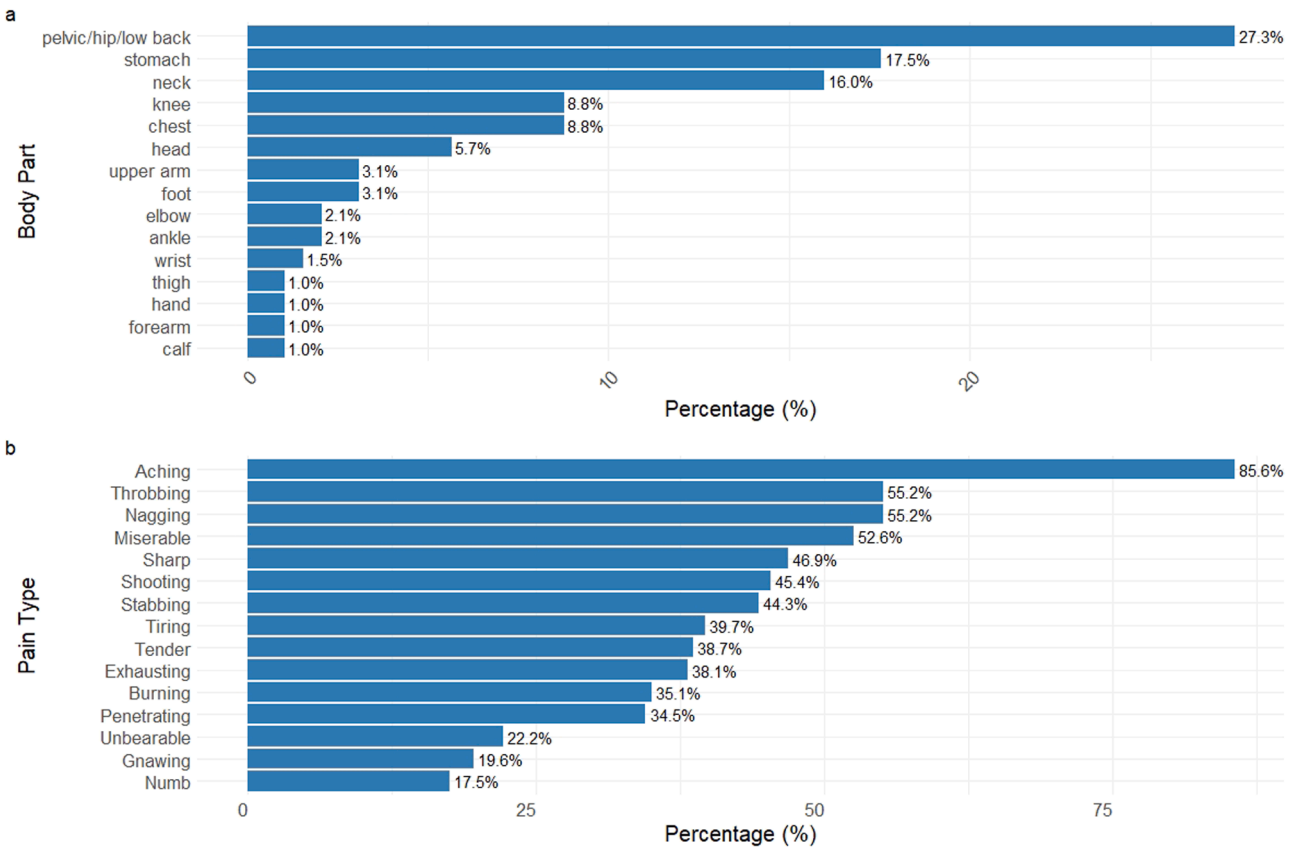

Fig. 1. a. Body parts most affected by pain. b. Subjective type of pain. *Note*: The total percentage for figure b exceeds 100 % because participants were allowed to select multiple descriptors for their pain type.

The level of daily kratom use in those with vs. without chronic pain

A total of 13,401 kratom-use events were reported among participants over 15 days, with a mean of 2.52 uses per participant per day. In an independent-samples t-test, there was no significant difference in daily frequencies of kratom use between those with chronic pain (M = 2.53, SEM = 0.10) and those without (M = 2.50, SEM = 0.08), t (347.76) = 0.24, $p = 0.81$, 95 % CI: −.22,.28.

Association between daily pain levels and kratom use frequency

The Poisson mixed-effects model indicated no significant association between daily pain levels and the frequency of kratom use ($B = -0.001$, $SE = 0.001$, $p = 0.312$, 95 % CI: −0.003, 0.001). A follow-up model showed that this effect was not significantly moderated by chronic-pain status ($B = 0.002$, $SE = 0.002$, $p = 0.398$, 95 % CI: −0.002, 0.006).

Association between kratom use since last report and current pain severity

The average current pain level, in random-prompt entries, was 19.2 (SD = 23.5; range: 0–100). In mixed-effects models, we found that during moments when participants reported using additional kratom since the last recorded use (suggesting they had used it more recently), pain levels were significantly lower compared to moments without additional use ($B = -1.81$, $SE = 0.61$, $p = 0.003$, 95 % CI: −3.01, −0.61). A follow-up model showed that this effect was not significantly moderated by chronic-pain status ($B = -0.24$, $SE = 1.23$, $p = 0.85$, 95 % CI: −2.66, 2.18).

Association between current levels of feeling kratom effects and pain severity

On average, the pain level in kratom-use follow-up entries (pain "since the last kratom use") was 17.2 (SD = 21.1; range: 0–100), and the level of currently feeling kratom effects was 62.8 (SD = 62.8; range: 0–100). Mixed-effects modeling indicated that during moments when participants felt more intense effects of kratom compared to their daily average, they reported lower pain levels since the last use ($B = -0.13$, $SE = 0.01$, $p < 0.001$, 95 % CI: −0.14, −0.11). The follow-up model, including chronic-pain status as a moderator, showed a significant interaction: compared to participants without chronic pain, participants with chronic pain showed stronger association between pain reduction and feeling kratom effects ($B = -0.14$, $SE = 0.04$, $p < 0.001$, 95 % CI: −0.17, −0.11). Fig. 6 illustrates this interaction effect.

Sensitivity analyses findings

Visual inspection of residuals from the mixed-effects models revealed some degree of non-normality and heteroscedasticity. Although mixed-effects models are generally robust to such violations,[27] we conducted sensitivity analyses by applying a square root transformation to the outcome variable to address potential concerns. The results of these analyses were consistent with the original findings, underscoring the robustness of the mixed-effects models to these assumption violations.

Specifically, regarding the relationship between kratom use since the last report and current pain severity, same as the original findings, participants who reported additional kratom use since their last recorded use had significantly lower pain levels compared to moments without additional use ($B = -0.13$, $SE = 0.07$, $p = 0.023$, 95 % CI: −0.31, −0.02). This effect was not significantly moderated by chronic pain status ($B = 0.08$, $SE = 0.15$, $p = 0.61$, 95 % CI: −0.21, 0.36).

Additionally, in terms of the relationship between current levels of feeling kratom effects and pain severity, same as the original findings, participants who experienced more intense kratom effects than their daily average reported significantly lower pain levels ($B = -0.02$, $SE = 0.00$, $p < 0.001$, 95 % CI: −0.02, −0.01). The moderation effect of chronic pain status remained significant ($B = -0.01$, $SE = 0.002$, $p < 0.001$, 95 % CI: −0.01, −0.007).

We also conducted sensitivity analyses to explore potential

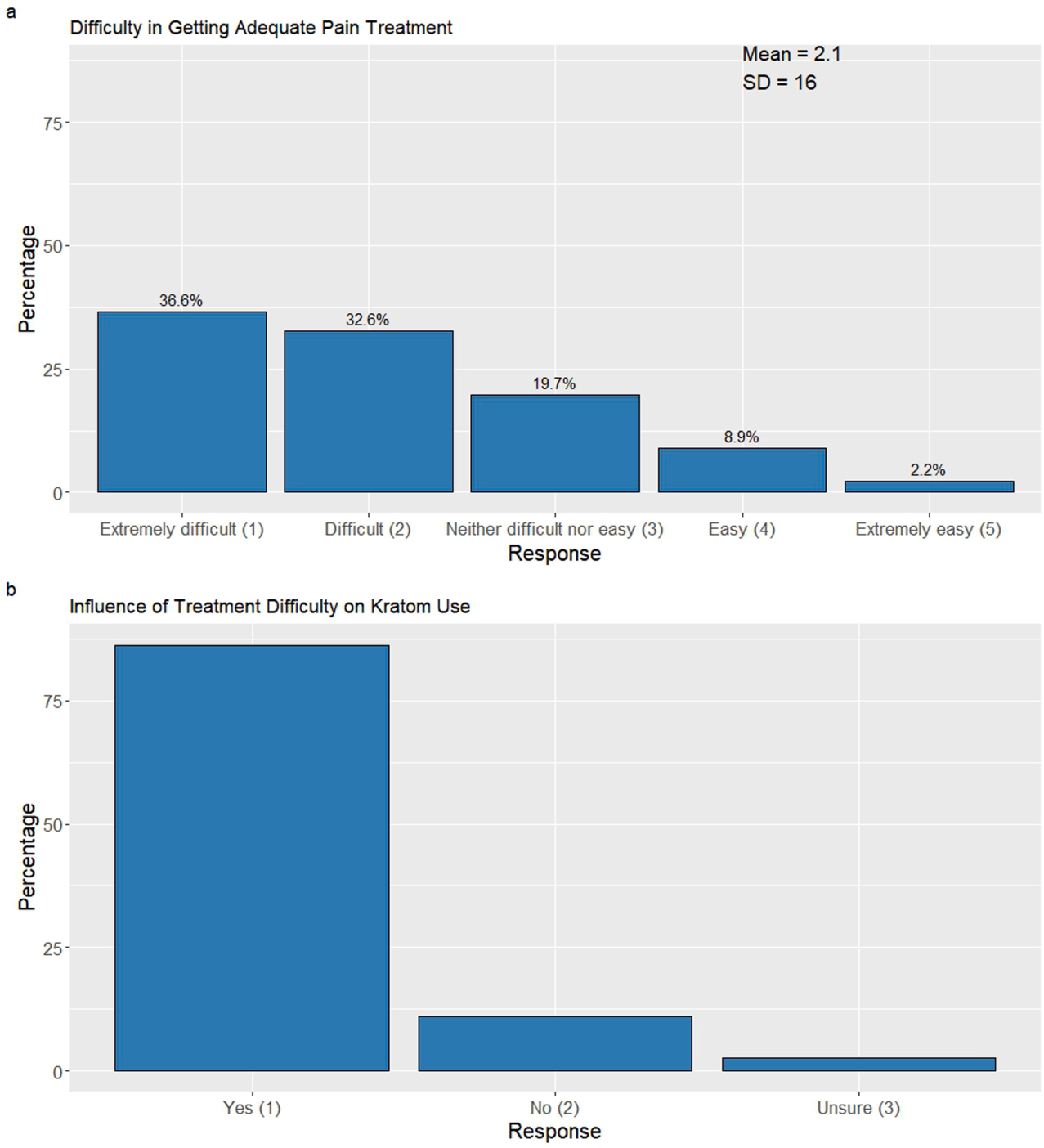

Fig. 2. a. Difficulty in getting adequate pain treatment. b. Influence of treatment difficulty on kratom use.

differences in the proportion of individuals with chronic pain and the average daily kratom use frequency between those residing in metro and non-metro areas. A chi-square test was used to assess the relationship between metro status and chronic pain, revealing no significant association ($\chi^2(1) = 0.25, p = 0.62$). Additionally, an independent samples t-test compared the average daily kratom use frequency between the metro and non-metro groups, showing no significant difference ($t(353) = 0.44, p = 0.66$). The mean daily kratom use frequency was 2.50 per day for individuals in metro areas and 2.58 per day for those in non-metro areas.

Discussion

This was the first comprehensive examination of pain symptoms and self-management of pain among a sample of US adults who regularly consume kratom. Although we recruited participants on the basis of kratom use, not pain, we found that nearly half (49.1 %) of participants met criteria for chronic pain. This is consistent with epidemiological estimates of the prevalence of chronic pain in kratom consumers (50.2–68.8 %).[28] Here, participants with chronic pain reported moderate levels of pain severity and interference, with the pelvic, hip, and back region being the most affected body parts. Interestingly, stomach pain was the second most commonly reported primary pain location in our

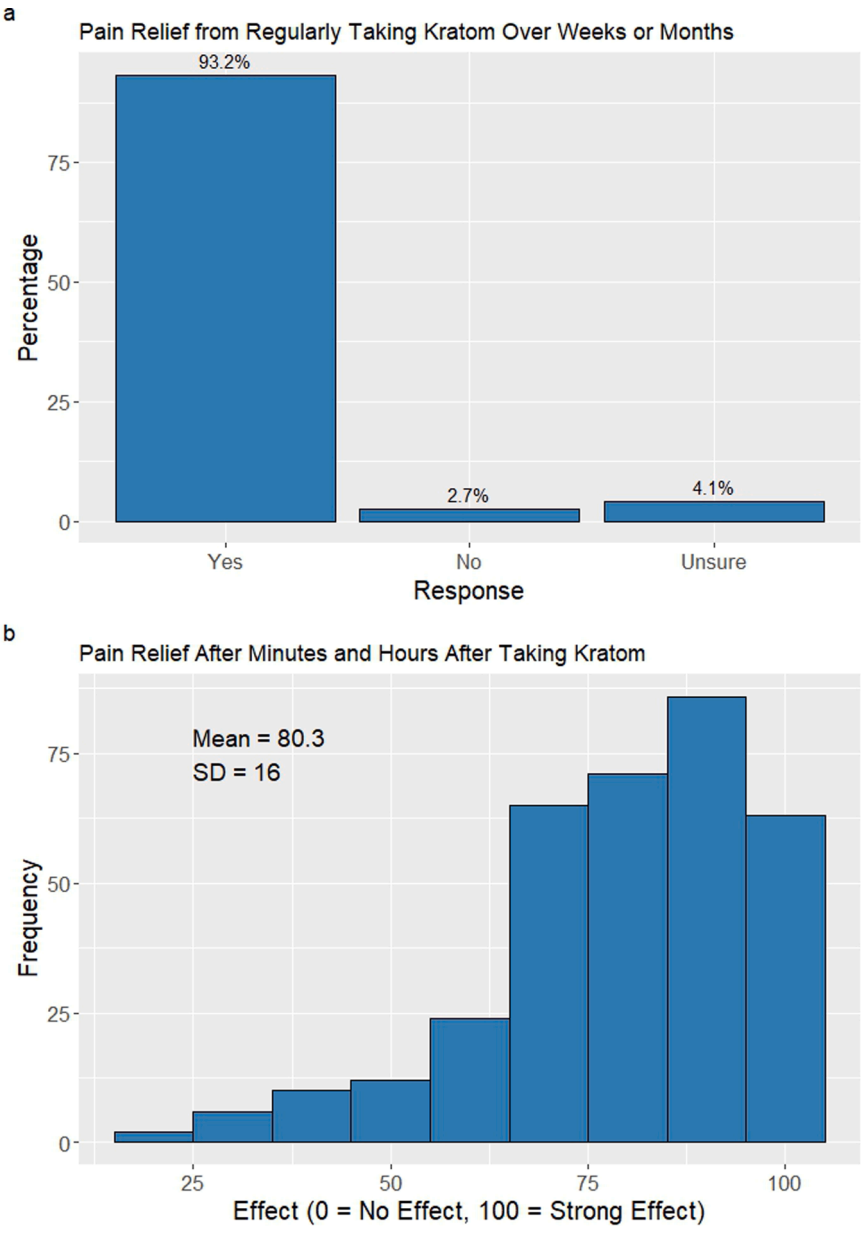

Fig. 3. a. Pain relief from regularly taking kratom over weeks or months. b. Pain relief after minutes and hours after taking kratom.

sample, which contrasts with recent epidemiological data.[29] While this discrepancy may be due to our study's use of convenience sampling rather than an epidemiological approach, we note that kratom has historically been used to manage diarrhea and stomach pain. This may explain why individuals with gastrointestinal-related pain are more likely to turn to kratom for pain management compared to the broader chronic pain population. Overall, participants indicated experiencing substantial pain relief and high effectiveness of kratom in self-managing both acute and chronic pain. These are consistent with kratom's analgesic profile in pre-clinical studies.[15–17,30,31]

The present study uniquely contributes to the literature by utilizing EMA data, which offers insights into kratom consumers' real-time motivations, usage patterns, subjective effects, and pain levels in real-world settings with minimization of recall bias.[32] Across a 15-day period, participants most frequently reported pain relief as their primary reason for using kratom, regardless of their chronic-pain status. Recent additional kratom use, assessed in near-real time, was significantly associated with reduced momentary pain levels. Additionally, greater subjective effects of feeling kratom were linked to lower pain levels since the last use, suggesting that pain relief is an important component of the perceived effects of kratom for many consumers, and/or that pain relief is highly correlated with kratom's other subjective effects. Those two interpretations, not mutually exclusive, require further study. The EMA findings were generally consistent with the results of our baseline survey and with findings from the only published human laboratory study to evaluate the analgesic effects of kratom, which demonstrated its efficacy on cold pain tolerance among healthy male chronic kratom consumers in Malaysia,[13] a part of the world where kratom is indigenous, has been used much longer than in the US, and in preparations not available to US consumers (e.g., fresh leaf). The convergence of findings from retrospective surveys and EMA (along with laboratory studies) suggests that kratom is perceived as analgesic within two different evaluative frameworks: the "experiencing self" of EMA, with its relatively unmediated access to the moment, and the more integrative "remembering self" of surveys that rely on retrospective recall.[33,34] In the assessment of any aspect of quality of life (here, living with chronic pain), each of these frameworks contributes crucial and distinct information—though neither is free from the belief-based effects that call for

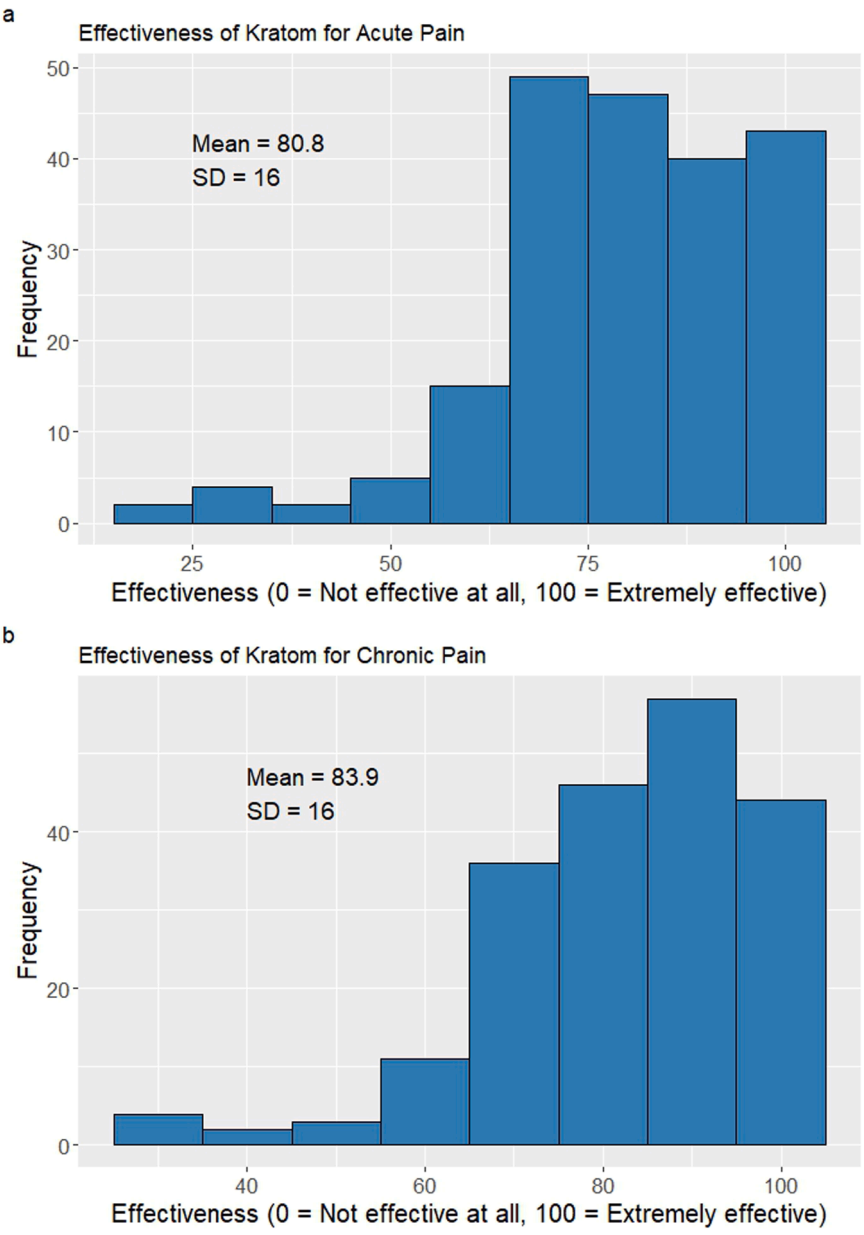

Fig. 4. a. Effectiveness of kratom for acute pain. b. Effectiveness of kratom for chronic pain.

placebo-controlled experiments.

Our findings also highlight the complex landscape of pain management in the US, with a substantial portion of participants trying kratom due to reported difficulties in accessing adequate pain treatments. Notably, the first peer-reviewed reports of kratom use in the US described its use for self-managing chronic pain (and self-treatment of opioid withdrawal by people with chronic pain).[35,36] Since then, kratom use appears to have persisted as a non-medical alternative for self-managing pain for many consumers, particularly those who have difficulty accessing pain treatment. Hence, kratom seems to be providing an alternative for some individuals who do not have adequate pain management access or who do not feel well served by standard pain-management practices.

Interestingly, as captured by the baseline survey, most participants in the present study did not report overusing kratom for pain management or experiencing significant side effects, although unwanted or adverse effects (e.g., nausea, constipation, and tolerance) from long-term kratom use have been noted among regular consumers.[37–39] Our EMA data also confirmed that higher daily pain levels were not significantly associated with greater kratom use frequency, and those with chronic pain do not use kratom significantly more than those without chronic pain. It is possible that people who use kratom regularly can titrate their dose to find a level that is effective and acutely well-tolerated as they self-manage acute or chronic pain.[39,40]

The effectiveness of kratom for pain management reported in this study and elsewhere[4,11,41] must be contextualized by the unknowns and the fact that, like any substance, kratom is not free from acute or chronic side effects. Prolonged use of kratom, especially at high doses, can result in the development of craving, tolerance, and withdrawal symptoms.[37,42,43] In fact, at least three recent studies, including two with large samples ($N > 2000$), report that a notable proportion (12.3 %–29.5 %) of kratom consumers met criteria for kratom use disorder, mostly of mild to moderate severity based on counts of criteria for substance use disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[37,44,45] Hence, there is a need for careful consideration and monitoring of kratom use for chronic pain self-management. Further research is also necessary to better understand kratom's long-term implications and to develop recommendations in light of the fact that there

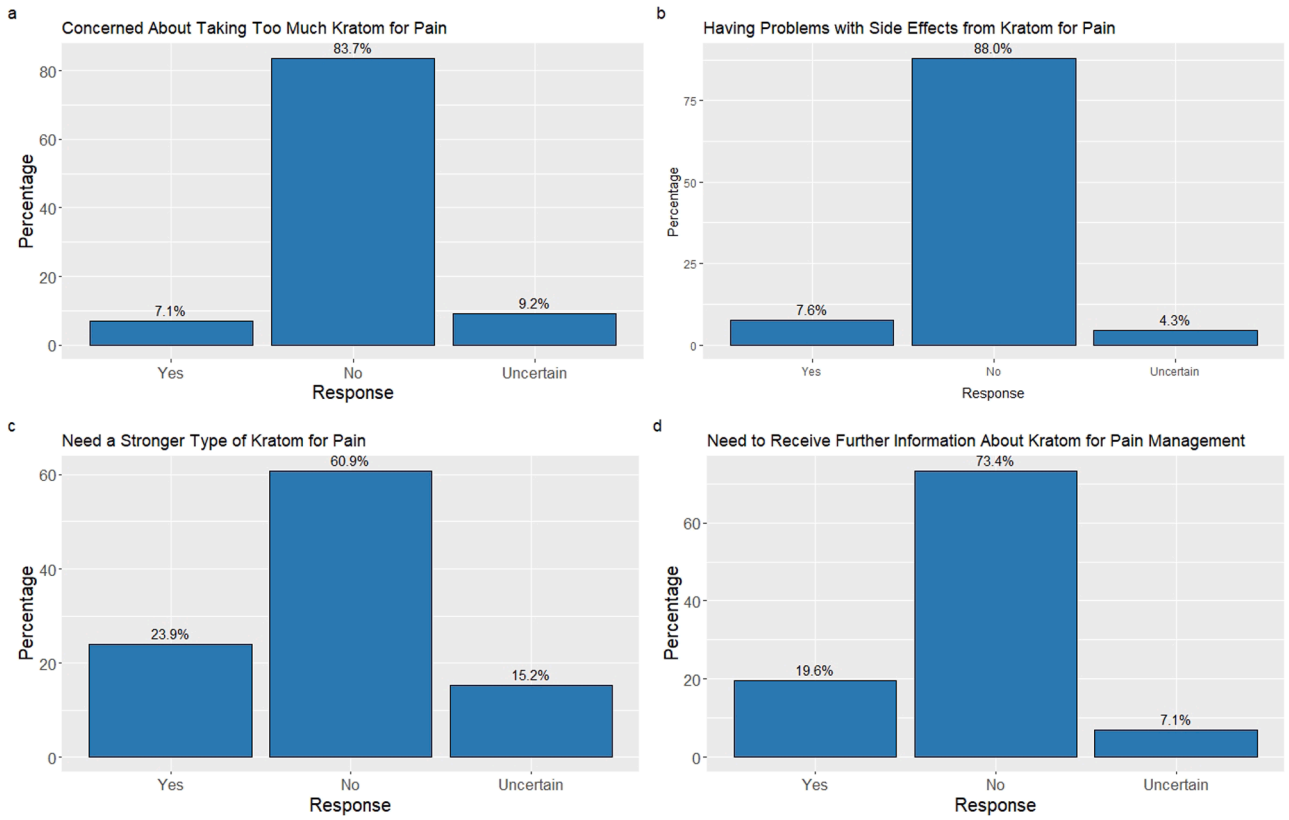

Fig. 5. a. Concern about taking too much kratom for pain. b. Having problems with side effects from kratom for pain. c. Need a stronger type of kratom for pain. d. Need to receive further information about kratom for pain.

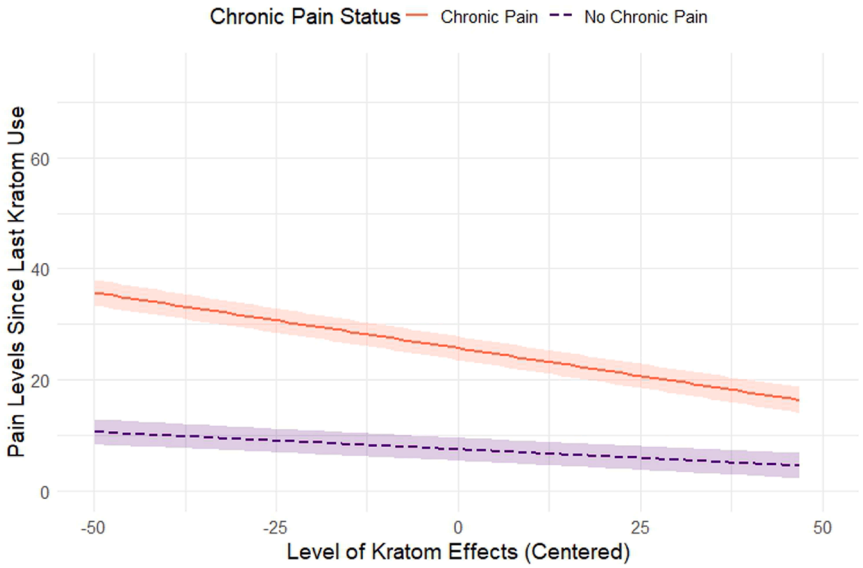

Fig. 6. Association between current levels of feeling kratom effects and pain severity moderated by chronic pain status. *Note*. Shaded areas indicate standard error bands with 95 % confidence intervals.

are, to date, no published safety data on kratom in humans. Our findings show that a significant proportion of US adults with chronic pain are turning to unregulated kratom products for self-managing their pain symptoms, and that at least a quarter of our sample reported needing a stronger type of kratom to manage their pain. This phenomenon is occurring despite FDA warnings about kratom and without much in the way of consumer guidance for use of kratom products. As kratom is not an FDA-approved new dietary ingredient, drug, or food, kratom vendors are limited in the information they can provide to consumers and the claims they can make. This appears to leave consumers on their own to share information and experiences.[41,46]

We strongly urge that future research include rigorous human laboratory studies on the safety and effectiveness of kratom and its constituent alkaloids for the symptoms for which consumers are using it. Chronic pain is overrepresented among kratom consumers, highlighting the importance of investigating its safety and effectiveness as an

analgesic, which has the potential to address critical gaps in current pain management strategies. However, conducting such trials presents significant challenges due to the inherent variability in kratom's preparation and composition. As a natural product derived from tree leaves, marketed kratom can vary widely in its formulation and total alkaloid content.[47–50] This variability can complicate dose standardization, which is important for clinical trials. Even if investigators were to source a standardized kratom whole-leaf formulation for submission of an Investigational New Drug application for research purposes with FDA, the results of that research may not generalize to all whole-leaf kratom formulations in the marketplace. There is not yet wide-scale standardization within kratom cultivation, and not all kratom vendors are Good Manufacturing Practices (GMP) certified. Additionally, one common method of kratom consumption—preparing a drink using leaf material[18,44]—adds another layer of complexity, particularly in creating an effective placebo control. These factors necessitate innovative methodologies and designs to ensure the rigor and reliability of clinical trials involving kratom, aiming to produce robust evidence about its therapeutic potential and safety profile.

Limitations

This study was not without limitations. First, we did not assess specific diagnostic criteria for chronic-pain conditions among participants. Having this information could have provided greater insight into our findings. For instance, it is possible that individuals with certain conditions, such as neuropathic pain, may benefit differently compared to those with other types of chronic pain (e.g., inflammatory or nociplastic pain). Second, our real-time assessment covered only 15 days. Although many of our participants had used kratom for years prior to the study, longitudinal studies are needed to examine the long-term within-person dynamics of perceived effects of kratom on pain. Third, the study's design cannot establish causality regarding the analgesic effects of kratom. Randomized-controlled trials are needed to establish causality. Fourth, the cross-sectional data, which depended on participants' retrospective recall, introduces the potential for recall bias and inaccuracies that could impact the external validity of the findings. Fifth, many of the measures used in this study were developed or adapted by the authors and have not yet undergone formal psychometric validation, which may limit the interpretability of certain findings. Lastly, the self-selected, potentially biased sample of regular kratom consumers may not represent the broader kratom consumer population, or people who tried kratom but did not continue to use it.

Conclusion

This study significantly contributes to the discourse on kratom's potential in self-management of chronic pain. Our findings emphasize the critical need for systematic and rigorous human research to thoroughly evaluate both the benefits and risks of kratom as a pain management strategy. Future research should also focus on uncovering the specific mechanisms behind kratom's analgesic effects, employing diverse and robust methodologies. Such research will be crucial in guiding informed clinical practices and regulatory policies.

Funding

Research was supported by the National Institute on Drug Abuse (NIDA) Intramural Research Program of the NIH and by NIDA grant DA055571 (KES), and National Institute of Neurological Disorders and Stroke (NINDS) grant R01NS129887 (CJM).

Declaration of Competing Interest

Within the past three years, KES has served as paid scientific advisor to the International Plant and Herbal Alliance and The Kratom Coalition. KES and CRM have served as expert witnesses in legal cases involving kratom. The remaining authors have no conflicts of interest to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpain.2024.104726.

References

1. Adkins JE, Boyer WE, McCurdy CR. Mitragyna speciosa, a psychoactive tree from Southeast Asia with opioid activity. *Curr Top Med Chem*. 2011;11(9):1165–1175.
2. Hassan Z, Muzaimi M, Navaratnam V, et al. From Kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. *Neurosci Biobehav Rev*. 2013;37(2):138–151.
3. Kruegel AC, Grundmann O. The medicinal chemistry and neuropharmacology of kratom: a preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. *Neuropharmacology*. 2018;134(Part A)):108–120.
4. Smith KE, Dunn KE, Rogers JM, et al. Kratom use as more than a "self-treatment. *Am J Drug Alcohol Abuse*. 2022;48(6):684–694.
5. Henningfield JE, Grundmann O, Huestis MA, Smith KE. Kratom safety and toxicology in the public health context: research needs to better inform regulation. *Front Pharmacol*. 2024;15, 1403140.
6. Henningfield JE, Grundmann O, Babin JK, Fant RV, Wang DW, Cone EJ. Risk of death associated with kratom use compared to opioids. *Prev Med*. 2019;128, 105851.
7. Swogger MT, Smith KE, Garcia-Romeu A, et al. Understanding kratom use: a guide for healthcare providers. *Front Pharmacol*. 2022;13, 801855.
8. Palamar JJ. Past-year kratom use in the US: estimates from a nationally representative sample. *Am J Prev Med*. 2021;61(2):240–245.
9. Coe MA, Pillitteri JL, Sembower MA, Gerlach KK, Henningfield JE. Kratom as a substitute for opioids: results from an online survey. *Drug Alcohol Depend*. 2019;202:24–32.
10. Grundmann O. Patterns of kratom use and health impact in the US—results from an online survey. *Drug Alcohol Depend*. 2017;176:63–70.
11. Grundmann O, Veltri CA, Morcos D, et al. Exploring the self-reported motivations of kratom (Mitragyna speciosa Korth.) use: a cross-sectional investigation. *Am J Drug Alcohol Abuse*. 2022;48(4):433–444.
12. Garcia-Romeu A, Cox DJ, Smith KE, Dunn KE, Griffiths RR. Kratom (Mitragyna speciosa): User demographics, use patterns, and implications for the opioid epidemic. *Drug Alcohol Depend*. 2020;208, 107849.
13. Vicknasingam B, Chooi WT, Rahim AA, et al. Kratom and pain tolerance: a randomized, placebo-controlled, double-blind study. *Yale J Biol Med*. 2020;93(2):229–238.
14. Kruegel AC, Uprety R, Grinnell SG, et al. 7-Hydroxymitragynine is an active metabolite of mitragynine and a key mediator of its analgesic effects. *ACS Cent Sci*. 2019;5(6):992–1001.
15. Hiranita T, Obeng S, Sharma A, Wilkerson JL, McCurdy CR, McMahon LR. In vitro and in vivo pharmacology of kratom. *Adv Pharmacol*. 2022;93:35–76. https://doi.org/10.1016/bs.apha.2021.10.001.
16. Obeng S, Kamble SH, Reeves ME, et al. Investigation of the adrenergic and opioid binding affinities, metabolic stability, plasma protein binding properties, and functional effects of selected indole-based kratom alkaloids. *J Med Chem*. 2020;63(1):433–439. https://doi.org/10.1021/acs.jmedchem.9b01465.
17. León F, Obeng S, Mottinelli M, et al. Activity of Mitragyna speciosa ("Kratom") alkaloids at serotonin receptors. *J Med Chem*. 2021;64(18):13510–13523. https://doi.org/10.1021/acs.jmedchem.1c00726.
18. Smith KE, Panlilio LV, Feldman JD, et al. Ecological momentary assessment of self-reported kratom use, effects, and motivations among US adults. *JAMA Netw Open*. 2024;7(1), E2353401. https://doi.org/10.1001/jamanetworkopen.2023.53401.
19. Smith KE, Feldman JD, Dunn KE, et al. Novel methods for the remote investigation of emerging substances: application to kratom. *Exp Clin Psychopharmacol*. 2024;32(2):215–227.
20. Merrill JE, Fan P, Wray TB, Miranda JrR. Assessment of alcohol use and consequences: comparison of data collected via timeline followback interview and daily reports. *J Stud Alcohol Drugs*. 2020;81(2):212–219.
21. Adams LB, Watts T, DeVinney A, et al. Acceptability and feasibility of a smartphone-based real-time assessment of suicide among Black men: mixed methods pilot study. *JMIR Form Res*. 2024;8, e48992.
22. Luken A, Rabinowitz JA, Wells JL, et al. Designing and validating a novel method for assessing delay discounting associated with health behaviors: ecological momentary assessment study. *JMIR Form Res*. 2024;8(1)), e48954.
23. Thrul J, Nordeck CD, Devkota J, et al. I crave not to feel uncomfortable'–investigating craving for opioids and cannabis among individuals with chronic pain. *Drugs Educ Prev Policy*. 2024. Online Ahead of Print.
24. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap*. 1994;23(2):129–138.
25. Calin-Jageman RJ, Cumming G. The new statistics for better science: ask how much, how uncertain, and what else is known. *Am Stat*. 2019;73(sup1):271–280.
26. Bürkner P-C. brms: an R package for Bayesian multilevel models using Stan. *J Stat Softw*. 2017;80:1–28.
27. Schielzeth H, Dingemanse NJ, Nakagawa S, et al. Robustness of linear mixed-effects models to violations of distributional assumptions. *Methods Ecol Evol*. 2020;11(9):1141–1152.

28. Farkas DJ, Cooper ZD, Heydari LN, Hughes AC, Rawls SM, Ward SJ. Kratom alkaloids, cannabinoids, and chronic pain: basis of potential utility and role in therapy. *Cannabis Cannabinoid Res*. 2023. https://doi.org/10.1089/can.2023.0064. Ahead of Print.
29. Yong RJ, Mullins PM, Bhattacharyya N. Prevalence of chronic pain among adults in the United States. *Pain*. 2022;163(2):e328–e332.
30. Fazalul Rahiman SS, Ballouze R, Mathandaver D, Al-Amin M, Salhimi SM. Opioid-like compounds isolated from Mitragyna speciosa, Picralima nitida and Clinacanthus nutans as potential therapeutics for peripheral analgesia via opioid and nonopioid mechanisms: a review. *Malays J Med Health Sci*. 2024;20:212–223 (supp1).
31. Shaik Mossadeq WM, Sulaiman MR, Tengku Mohamad TA, et al. Anti-inflammatory and antinociceptive effects of Mitragyna speciosa Korth methanolic extract. *Med Princ Pract*. 2009;18(5):378–384.
32. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. *Annu Rev Clin Psychol*. 2008;4(1):1–32.
33. Redelmeier DA, Kahneman D. Patients' memories of painful medical treatments: real-time and retrospective evaluations of two minimally invasive procedures. *Pain*. 1996;66(1):3–8.
34. Kahneman D, Riis J. *Living, and thinking about it: two perspectives on life. The science of well-being*. UK: Oxford University Press; 2005:285–304. https://doi.org/10.1093/acprof:oso/9780198567523.003.0011.
35. Boyer EW, Babu KM, Macalino GE, Compton W. Self-treatment of opioid withdrawal with a dietary supplement, Kratom. *Am J Addict*. 2007;16(5):352–356.
36. Boyer EW, Babu KM, Adkins JE, McCurdy CR, Halpern JH. Self-treatment of opioid withdrawal using kratom (Mitragynia speciosa korth). *Addiction*. 2008;103(6):1048–1050.
37. Smith KE, Dunn KE, Rogers JM, Garcia-Romeu A, Strickland JC, Epstein DH. Assessment of kratom use disorder and withdrawal among an online convenience sample of US adults. *J Addict Med*. 2022;16(6):666–670.
38. Smith KE, Rogers JM, Dunn KE, et al. Searching for a signal: self-reported kratom dose-effect relationships among a sample of US adults with regular kratom use histories. *Front Pharmacol*. 2022;13, 765917.
39. Smith KE, Feldman JD, Dunn KE, et al. Examining the paradoxical effects of kratom: a narrative inquiry. *Front Pharmacol*. 2023;14, 1174139.
40. Rogers JM, Weiss ST, Epstein DH, Grundmann O, Hill K, Smith KE. Kratom addiction per DSM-5 SUD criteria, and kratom physical dependence: insights from dosing amount versus frequency. *Drug Alcohol Depend*. 2024;260, 111329.
41. Smith KE, Rogers JM, Schriefer D, Grundmann O. Therapeutic benefit with caveats?: Analyzing social media data to understand the complexities of kratom use. *Drug Alcohol Depend*. 2021;226, 108879.
42. Stanciu CN, Gnanasegaram SA, Ahmed S, Penders T. Kratom withdrawal: a systematic review with case series. *J Psychoact Drugs*. 2019;51(1):12–18.
43. Singh D, Müller CP, Vicknasingam BK. Kratom (Mitragyna speciosa) dependence, withdrawal symptoms and craving in regular users. *Drug Alcohol Depend*. 2014;139:132–137.
44. Hill K, Grundmann O, Smith KE, Stanciu CN. Prevalence of kratom use disorder among kratom consumers. *J Addict Med*. 2024;18(3):306–312.
45. Bath R, Bucholz T, Buros AF, et al. Self-reported health diagnoses and demographic correlates with kratom use: results from an online survey. *J Addict Med*. 2020;14(3):244–252.
46. Rogers JM, Colvin K, Epstein DH, Grundmann O, McCurdy CR, Smith KE. Growing pains with kratom: experiences discussed in subreddits contrast with satisfaction expressed in surveys. *Front Pharmacol*. 2024;15, 1412397.
47. Zhang M, Sharma A, León F, et al. Plant growth and phytoactive alkaloid synthesis in kratom [Mitragyna speciosa (Korth.)] in response to varying radiance. *PLoS One*. 2022;17(4), e0259326.
48. Phromchan W, Defri I, Saensano C, Chookaew A, Chiarawipa R, Sriwiriyajan S. Morphological and physiological properties of kratom (Mitragyna speciosa) leaves: macronutrients, phytochemicals, antioxidants, and mitragynine content. *Plant Sci Today*. 2024;11(2):762–770.
49. Leksungnoen N, Andriyas T, Ngernsaengsaruay C, et al. Variations in mitragynine content in the naturally growing Kratom (Mitragyna speciosa) population of Thailand. *Front Plant Sci*. 2022;13, 1028547.
50. Huisman G, Menke M, Grundmann O, Schreiber R, Mason N. Examining the psychoactive differences between kratom strains. *Int J Environ Res Public Health*. 2023;20(14):6425.