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ORIGINAL INVESTIGATION

An exploratory study of the safety profile and neurocognitive function after single doses of mitragynine in humans

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Abstract

Rationale Despite the growing scientific interest on mitragynine, the primary alkaloid in kratom (*Mitragyna Speciosa*), there is a lack of clinical trials in humans.

Objectives This phase 1 study aimed to evaluate mitragynine's safety profile and acute effects on subjective drug experience, neurocognition, and pain tolerance.

Methods A placebo-controlled, single-blind, within-subjects study was conducted in two parts. In part A, eight healthy human volunteers received placebo and three doses of mitragynine (5, 10, and 20 mg) in a sequential dosing scheme, on separate days. In part B, a second group of seven volunteers received placebo and 40 mg of mitragynine. Vital signs, subjective drug experience, neurocognitive function, and pain tolerance were measured at regular intervals for 7 h after administration.

Results Overall, mitragynine did not affect most of the outcome measures at any dose. Yet, the lowest dose (5 mg) of mitragynine increased subjective ratings of arousal and attention, accuracy in a sustained attention task, and motor inhibition. The highest dose (40 mg) of mitragynine increased subjective ratings of amnesia and produced mild psychopathological symptoms. Mitragynine did not significantly affect vital signs, and only mild, transient side effects were reported.

Conclusion The present study suggests that low doses (5–10 mg) of mitragynine may cause subjective feelings of stimulation and enhance attention, while the highest dose (40 mg) may cause inhibitory feelings of amnesia and distress. Mitragynine doses up to 40 mg were well tolerated in this group.

Keywords Kratom · Mitragynine · *Mitragyna speciosa* · Pain · Acute effects · Safety · Neurocognition · Placebo-controlled study

Introduction

Kratom is a plant known as *Mitragyna Speciosa (Rubiaceae Family)*, naturally growing in Africa, South-East Asia (e.g., Malaysia and Thailand), and New Guinea. Since the 19th century, its leaves and extracts have been used as a folk remedy in these countries to deal with common health problems (e.g., pain, fever, diabetes), to replace opiates, and to boost energy and reduce fatigue (Cinosi et al. 2015; Hassan et al. 2013; Kruegel and Grundmann 2018; Swogger et al. 2022).

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Kratom use has also expanded to Western countries, leading to a wide availability of kratom products (e.g., powder, capsules, tablets) online and in specialty shops (Hillebrand et al. 2010; Prevete et al. 2024; Prozialeck et al. 2012; Williams and Nikitin 2020). The main motivations for using kratom include recreational purposes and self-treatment of various mental and physical health conditions (Bath et al. 2020; Coe et al. 2019; Grundmann et al. 2022, 2023; Smith et al. 2024a). A small amount (< 5 g) of raw plant material has been reported to produce stimulatory effects such as increasing talkativeness, alertness, or physical energy (Henningfield et al. 2024; Kruegel and Grundmann 2018; Prozialeck et al. 2012; Singh et al. 2019a; Swogger et al. 2022). Doses above 5 g have been reported to produce inhibitory-analgesic and sedative properties like opioids (Henningfield et al. 2024; Kruegel and Grundmann 2018; Prozialeck et al. 2012; Singh et al. 2019a; Swogger et al. 2022). Moreover, it has been shown that kratom's stimulant and sedative effects can co-exist (Smith et al. 2023a), often at higher doses (Peran et al. 2023).

The primary psychoactive alkaloid in kratom is mitragynine. This compound and its metabolite 7α-hydroxy-7 H-mitragynine are partial μ-opioid receptor agonist and competitive antagonist at κ- and δ-opioid receptors. In contrasts to classical opioids, mitragynine and 7-hydroxymitragynine also bind to adrenergic (α1 and α2) and serotonergic (5-HT1A and 5-HT2B) receptors (Henningfield et al. 2024; Hiranita et al. 2022; Kruegel et al. 2016; Kruegel and Grundmann 2018; Obeng et al. 2020, 2022; Raffa et al. 2018). In regular kratom users, the estimated, daily dose of mitragynine can typically range between 75 and 435 mg divided over 3 to 4 glasses of kratom juice (Leong Abdullah et al. 2021; Singh et al. 2018). In Western countries, kratom users typically consume between three and eight grams of raw plant material (Smith et al. 2022). However, kratom products might have variable mitragynine concentrations, making it hard to estimate a typical mitragynine dose. Mitragynine's pharmacokinetic profile has been studied in preclinical research (Ramachandram et al. 2019; Ya et al. 2019) and in humans (Huestis et al. 2024). In the latter study, 12 participants received dried kratom leaf powder capsules (500–4000 mg) containing between 6.65 and 53.2 mg of mitragynine. The median mitragynine T_{max} was 1.0–1.3 h after single and 1.0–1.7 h after multiple doses; for 7-hydroxymitragynine T_{max}, it was 1.2–1.8 h and 1.3–2.0 h. Steady-state mitragynine concentrations were reached in 8–9 days and 7-hydroxymitragynine within 7 days. Clinical data consistently indicate that mitragynine fits a two-compartment model when orally administered (Tanna et al. 2022; Trakulsrichai et al. 2015). Following 10–20 min, individuals may experience initial euphoric effects, which are reported to reach their peak intensity within 0.5–1 h, and can last 5 to 7 h (Prozialeck et al. 2012; Rosenbaum et al. 2012; Scott et al. 2014; Warner et al. 2016). Knowledge of adverse effects of kratom is scarce and mainly comes from user reports on drug fora and case reports that have suggested risks of dependence, withdrawal, cardiorespiratory problems, and kidney and liver injury (Alsarraf et al. 2019; Corkery et al. 2019; Peran et al. 2023; Schimmel and Dart 2020). However case reports often lack thoroughness because they may not provide a full assessment of the patient's kratom use (Feldman et al. 2023). Systematic reviews of case reports (Smith et al. 2023b) and in-depth interviews (Smith et al. 2023a) with chronic kratom users confirmed risk of dependence, while the latter also identified feelings of jitter at high doses.

To our knowledge, little comprehensive research has been conducted to evaluate the acute effects of mitragynine on measures of safety and neurocognition in healthy volunteers. A recent observational study in 10 chronic kratom users revealed only minor changes in vital signs and mild increments of euphoria after self-administration of 5.16 g (on average) of kratom leave powder (Smith et al. 2024b). Self-reported ($n = 357$) and simulated driving reports ($n = 10$) have suggested that kratom effects at self-selected doses among regular kratom consumers do not produce significant changes in subjective and objective measures of driving impairment (Zamarripa et al. 2024). However, systematic, controlled studies with mitragynine are presently missing. Thus, the main objective of this study was to evaluate mitragynine's safety profile in healthy participants through a placebo-controlled phase 1 trial with escalating doses. The secondary objectives were to evaluate mitragynine's pharmacokinetic profile and its acute effects on neurocognitive measures and pain tolerance. Based on previous reports on stimulant and sedative effects of kratom (Kruegel and Grundmann 2018; Prozialeck et al. 2012; Singh et al. 2019a; Swogger et al. 2022), the doses of mitragynine used in this study (i.e., 5, 10, 20, and 40 mg) were expected to produce similar, but dose-dependent effects.

Materials and methods

Participants

Twenty-two healthy volunteers were recruited for this study by word-of-mouth and via advertisements posted on local newspapers or websites and placed in Maastricht University buildings. The CONSORT diagram showing the flow of participants through each stage of this study is reported in Fig. S1. Fifteen participants entered and completed part A ($N = 8$ (3 females); 24.1 ± 2.7 years (mean ± SD)) or part B ($N = 7$ (5 females); 23.8 ± 1.9 years) of the study. Complete details

on demographic data and drug use history are depicted in Table S1. Only 2 out 15 participants had prior experience with kratom. A complete list of inclusion and exclusion criteria is provided in the supplement (S1). Of note, use of medication was not permitted, except for paracetamol. Candidate participants with a history of drug abuse were excluded.

Design and treatments

This interventional study followed a phase-1, placebo-controlled, single-blind, within-subjects design. In part A, eight participants received placebo and three doses (5, 10 and 20 mg) of mitragynine on separate test days. In part B, a second group of seven subjects received placebo and mitragynine (40 mg) on separate test days. Test days were separated by at least a 5-day washout period to avoid carryover effects. Tests conducted on test days were identical in parts A and B. Treatment was administered orally, with (synthetic) mitragynine powder dissolved in 200 mL of bitter lemon drink. For a placebo, only the bitter lemon drink was used. To ensure safety, an escalating dosing scheme was employed in part A, wherein each higher dose was given only after the completion of the previous lower dose. The placebo condition was balanced across treatment days. Participants were blind to the order of mitragynine and placebo administrations. An independent Study Safety Group (SSG) evaluated safety and behavioral data collected throughout the study. Interim SSG evaluations of vital signs and behavioral data were performed after completion of every block of 4 participants in each active treatment condition (mitragynine 5, 10, 20, and 40 mg). Stopping rules focussed on clinically relevant deviations in vital signs, relative to normal ranges.

The choice of the dose range (5–40 mg) in our study was guided by a controlled pharmacokinetic study in humans suggesting that mitragynine is safe in the range between 10 and 20 mg per day (Trakulsrichai et al. 2015), with oral intake known to be the most common way of consumption (Cinosi et al. 2015; Hassan et al. 2013; Wang and Walker 2018). In addition, the dose range overlapped with the estimated amount of mitragynine reported in single kratom drinks (i.e., 20–100 mg mitragynine) of regular kratom users (Leong Abdullah et al. 2021; Singh et al. 2018). Given that there had been no studies that assessed synthetic mitragynine in naive users, we opted to focus on low doses of mitragynine, rather than high doses that are sometimes taken by chronic users. The current dose range however overlaps with those currently expected in a variety of kratom products that are sold for recreational use (Prevete et al. 2024) and with those in kratom products that are currently under development for medical applications (Huestis et al. 2024).

This study was approved by the Dutch Central Committee on Research Involving Human Subjects (CCMO) and the Medical Ethics Committee of the Academic Hospital of Maastricht and Maastricht University (METC). It was carried out following the principles of Good Clinical Practice (GCP), the Medical Research Involving Human Subjects Act (WMO), and the code of ethics on human experimentation established by the declaration of Helsinki (1964), amended in Fortaleza (Brazil, October 2013). The study was registered in the Dutch CCMO-register (NL73317.068.20).

Procedures

Before inclusion, participants were invited for a screening, where they were asked for their medical history and drug use and received medical, physical, and psychological evaluations by a medical doctor, who checked general health (including vital signs (VS) and electrocardiogram (ECG)), blood and urine samples for routine laboratory tests (i.e., standard chemistry, serology, urinalyses, and haematology, including thyroid function test), drug and pregnancy screening (for females). The complete inclusion/exclusion criteria list is reported in Supplementary Materials. All participants gave their written informed consent and received a monetary remuneration plus a travel reimbursement for their participation. Before the test days, participants were invited for a training session to receive an explanation of test procedures and to familiarise them with neurocognitive tests. Before each experimental day, they were asked to refrain from any recreational drug for 7 days, to avoid using alcohol on the test day or the day prior to testing, and to avoid using other medicinal drugs (except paracetamol, painkillers, and oral contraceptives). On each test day, participants were asked to have a light breakfast (without fatty foods and caffeine) at home and to arrive well-rested at the test facilities. Smoking and caffeine were not allowed during the test day. Participants stayed in a quiet lab where they could relax in between testing. Upon arrival, an intravenous cannula for taking blood samples was placed. Baseline urine and blood samples (for laboratory safety and PK) were collected, and alcohol breathalyzing and urine drug screens were performed. In case of a positive screen for drugs (e.g., cocaine, alcohol, marijuana, opiates, benzodiazepine, methamphetamine, or amphetamine), participants were sent home to return to the laboratory another day. Women were also tested for pregnancy. Only when these tests were negative, the treatment was administered. After administration, safety parameters and measures or questionnaires related to drug experience, pain tolerance, and neurocognition were assessed at regular intervals up until 7 h after treatment. In

the same timeframe, and at the end of the test day, additional urine and blood samples were taken for both PK and laboratory safety assessment. At the end of the test day, the medical doctor determined whether the participant could return home or if they had to be kept under supervision until the side effects disappeared. A schematic representation of the timeline of the course of a test day is given in Table S2.

Safety measures, adverse events and follow-up

For safety reasons, a medical doctor was present, and VS (body temperature (BT), systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR), respiratory rate (RR), and peripheral capillary Oxygen Saturation (SpO2)) were measured at baseline and regular intervals after treatment administration (for more details and timing, see Table S2) until the end of the test day. Blood and urine samples for clinical laboratory safety (haematology, clinical chemistry, and urinalysis) were taken at baseline and the end of each test day.

Further, all participants received a diary and were requested to note all adverse events (AEs) during the test day and up until 120 h (5 days) after drug administration, to assess potential residual effects of mitragynine over subsequent days. All AEs reported either spontaneously or after questioning during the whole trial period were collected.

Drug experience and subjective measures

The Drug Effects Questionnaire (DEQ) (Morean et al. 2013) and Visual Analogue Scales (VAS) were used to assess the intensity of the drug experience (Holze et al. 2020). The acute effects of mitragynine on psychological state and mood were assessed with the Addiction Research Center Inventory (ARCI) (Haertzen et al. 1963; Martin et al. 1971), the Clinician-Administered Dissociative State Scale (CADSS) (Bremner 2014; Bremner et al. 1998), the Profile of Mood States (POMS) (de Wit et al. 2002; Pollock et al. 1979), and the Brief Symptom Inventory (BSI) (Derogatis 1975, 1993; Derogatis and Melisaratos 1983). Self-ratings of impulsivity were measured at 3 h after administration with the Barratt Impulsiveness Scale version 11 (BIS-11) (Barratt 1993; Patton et al. 1995; Stanford et al. 2009), the Adult ADHD Self-Report Scale (ASRS) (Daigre Blanco et al. 2009), and the Quick Delay Questionnaire (QDQ) (Clare et al. 2010).

Pain perception and neurocognition

The effect of mitragynine on pain tolerance was evaluated by administering the cold pressor test (CPT) (Silverthorn and Michael 2013), and subjective ratings of painfulness, unpleasantness, and stress.

Cognitive performances were evaluated with a battery of cognitive tests, including the Matching Familiar Figures Test (MFFT) (Cairns and Cammock 1978), the Stroop Color and Word Test (SCWT) (Lamers et al. 2010), the Digit-Symbol Substitution Task (DSST) (Jaeger 2018), the Stop-Signal Task (SST) (Verbruggen and Logan 2008), the Psychomotor Vigilance Task (PVT) (Loh et al. 2004), and the Prospective Memory Task (PMT) (Ramaekers et al. 2009).

A full description of each questionnaire, tests/tasks, the dependent variables, and their timing (Table S2) is provided in the Supplementary Materials.

Pharmacokinetic assessment

Blood samples to determine mitragynine concentrations in plasma were collected at baseline, and + 1, +3, and + 7 h after drug administration. Samples were centrifuged and serum was stored frozen. Analysis of mitragynine and 7-hydroxy-mitragynine in serum (200 µl) was performed after extraction with ethyl acetate/methyl tert-butyl ether (80:20, v/v) using liquid chromatography-tandem mass spectrometry (LC-MS/MS; Agilent, Waldbronn, Germany). Calibration curves covered the range 0.2–200 (mitragynine) and 0.1–100 (7-hydroxy-mitragynine) ng/ml with lower limits of quantitation (LLOQ) of 0.10 (mitragynine) and 0.09 (7-hydroxy-mitragynine) ng/ml.

Statistical analysis

A general linear model (GLM) repeated measures analysis of variance (ANOVA) was used to analyze the effects of mitragynine on all dependent measures. The main factors for the GLM were Drug (four levels in part A, i.e., placebo, mitragynine 5, 10, 20 mg; two levels in part B, i.e., placebo and mitragynine 40 mg), Time, and the interaction between Drug and Time. A *p-value* of ≤ 0.05 was considered statistically significant. The Greenhouse-Geisser correction was used in case of violation of the sphericity assumption. Post-hoc analyses/contrasts were always conducted in part A, irrespective of the main Drug effect. Bonferroni correction was not applied given the exploratory nature of the study. All statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 27.0.

Results

Missing data

Due to technical malfunctions, there was some missing data for subjective and neurocognitive measures in parts A and B. These were treated as missing values in our statistical analyses. Blood samples in part B were missing due to technical storage issues.

Safety measures and adverse events

Clinical chemistry, hematology, and urinalyses did not show significant changes or clinically relevant deviations from normal ranges in either condition for both parts of the study. Vital signs were well within the normal range across all treatments.

GLM analyses revealed no significant main effects of Drug and Drug by Time on measures of blood pressure, respiratory rate, body temperature, heart rate, and SpO2 in parts A and B. Drug-placebo contrast analyses showed that, compared to placebo, mitragynine 10 mg significantly decreased systolic blood pressure ($F_{1,6}$=7.552, p=.033, ηp^2 = 0.557), 20 mg caused a significant reduction in respiratory rate ($F_{1,7}$=5.691, p=.048, ηp^2 = 0.448), and in diastolic blood pressure ($F_{1,\ 6}$=7.446, p=.034, ηp^2 = 0.554) as shown by Drug by Time interactions. Similarly, 40 mg caused a slight decrease in diastolic blood pressure as shown by a Drug by Time interaction ($F_{1,4}$=7.258, p=.054, ηp^2 = 0.645).

In part A, no one reported AEs or serious AEs. In part B, minor AEs (fatigue, headache, dizziness, drowsiness/sleepiness, itching/burning sensation while urinating) were reported that resolved spontaneously. A summary of AEs is given in Table S3.

Mean (SE) for SBP, DBP, HR and RR are presented in Fig. 1, while BT and SpO2-related means are reported in Table S4.

Drug experience and subjective measures

GLM analyses (Drug and Drug by Time interaction) showed that mitragynine in parts A and B did not generate any significant subjective drug experience of *feel drug effects*, *high*, *like*, *good/bad effects*, and *wanting*, assessed through the VAS method and DEQ questionnaire (see Tables S4-S5). Drug-placebo contrasts also revealed no significant differences.

Further, GLM analyses (Drug and Drug by Time) showed that mitragynine did not generate any significant effect on the ARCI scales in parts A and B. Drug-placebo contrast analyses however revealed that mitragynine 5 mg and 10 mg significantly increased scores on the Amphetamine (A) ($F_{1,7}$=7.251, p=.031, ηp^2 = 0.509; $F_{1,7}$=7.000, p=.033, ηp^2 = 0.500) scale, with 5 mg also increasing rating on the Morphine Benzedrine Group (MBG) ($F_{1,7}$=9.215, p=.019, ηp^2 = 0.568) scale in comparison to placebo.

GLM analyses showed no significant main effects of Drug and Drug by Time on the CADSS total dissociative score and subscales (depersonalization, derealisation, and amnesia) in parts A and B. However, drug-placebo contrasts revealed that mitragynine 40 mg increased the score of the CADSS subscale Amnesia ($F_{1,6}$=6.194, p=.047, ηp^2 = 0.508).

GLM analyses showed no significant main effects of Drug and Drug by Time on the BSI dimensions (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism), and indices of distress (Global Severity Index, Positive Symptom Distress Index, and Positive Symptom Total) in parts A and B. Drug-placebo contrasts also revealed no significant differences in terms of BSI-related measures, with the exception of the BSI Obsession-Compulsion dimension, as GLM showed a Drug by Time interaction for mitragynine 40 mg, suggesting an increasing score over time after this dose ($F_{1,5}$=8.448, p=.034, ηp^2 = 0.628).

Moreover, according to GLM (Drug and Drug by Time) analyses no significant findings in terms of impact on mood states (POMS) were demonstrated for parts A and B, neither drug-placebo contrast analyses revealed significant differences.

Mean (SE) values for the BSI Obsession-Compulsion subscale, CADSS amnesia, ARCI A, and MBG scales are presented in Fig. 2.

Finally, GLM analyses showed no main effects of Drug or Drug by Time on impulsivity as measured with BIS-11, ASRS, and QDQ scales in part A and B. GLM drug-placebo contrast analyses showed an increase in the sub-factor cognitive instability of the BIS-11 ($F_{1,7}$=11.667, p=.011, ηp^2 = 0.625) after 5 mg of mitragynine, while 40 mg induced a significant increase in ASRS impulsivity symptoms ($F_{1,7}$=7.353, p=.042, ηp^2 = 0.595). Drug-placebo contrast analyses did not reveal other significant effects of mitragynine on impulsivity as measured with BIS-11, ASRS, and QDQ scales in both parts of the study.

For statistics of all the measures mentioned in this section see Tables S4-S5.

Pain perception

GLM analyses showed that mitragynine did not generate any significant effect on pain perception as measured by the CPT and VAS-related pain in part A and B. Drug-placebo

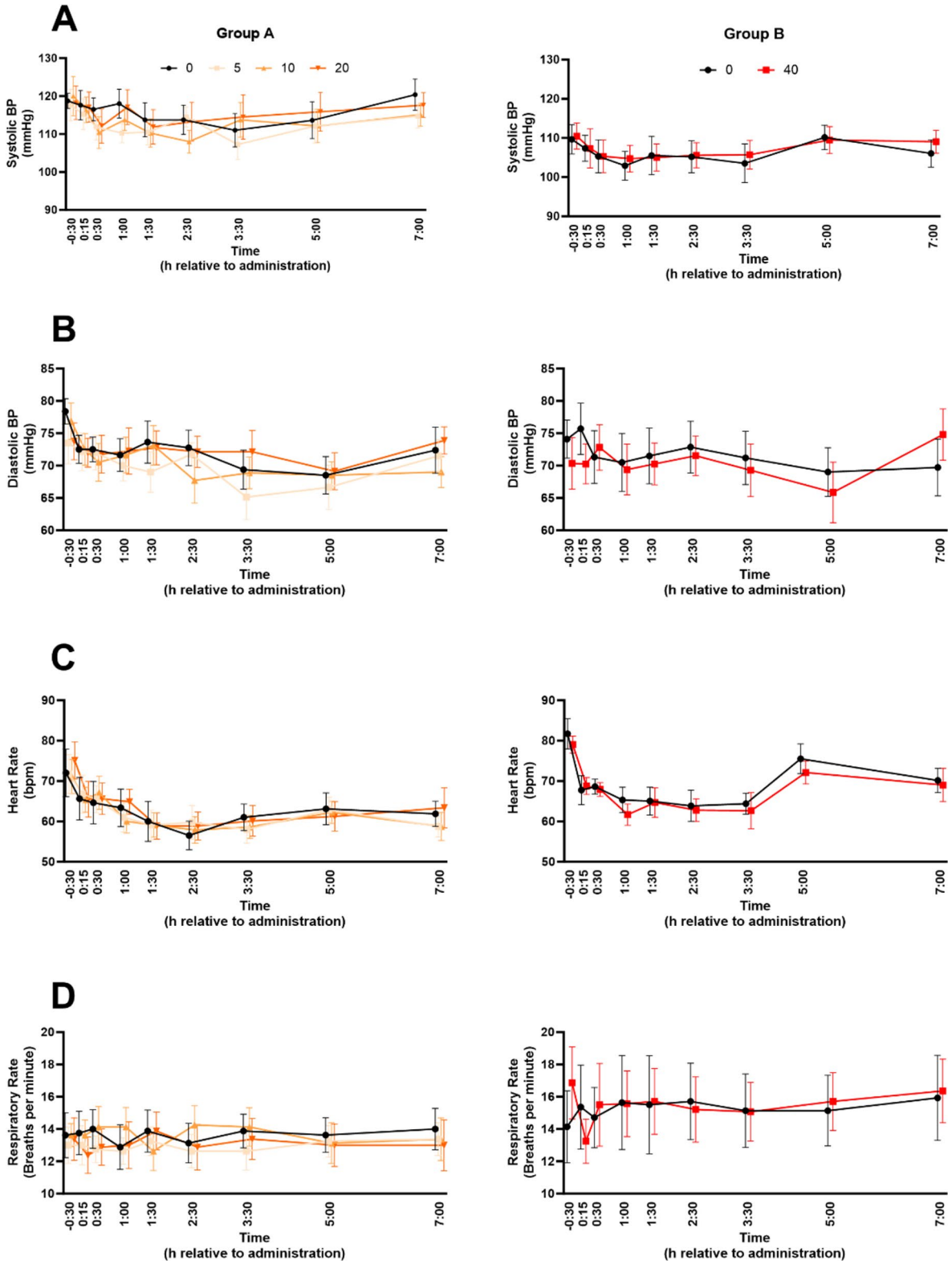

Fig. 1 Mean (SE) for Systolic Blood Pressure (**A**), Diastolic Blood Pressure (**B**), Heart Rate (**C**), and Respiratory Rate (**D**) measured at the baseline and regular intervals after drug administration in both parts of the study

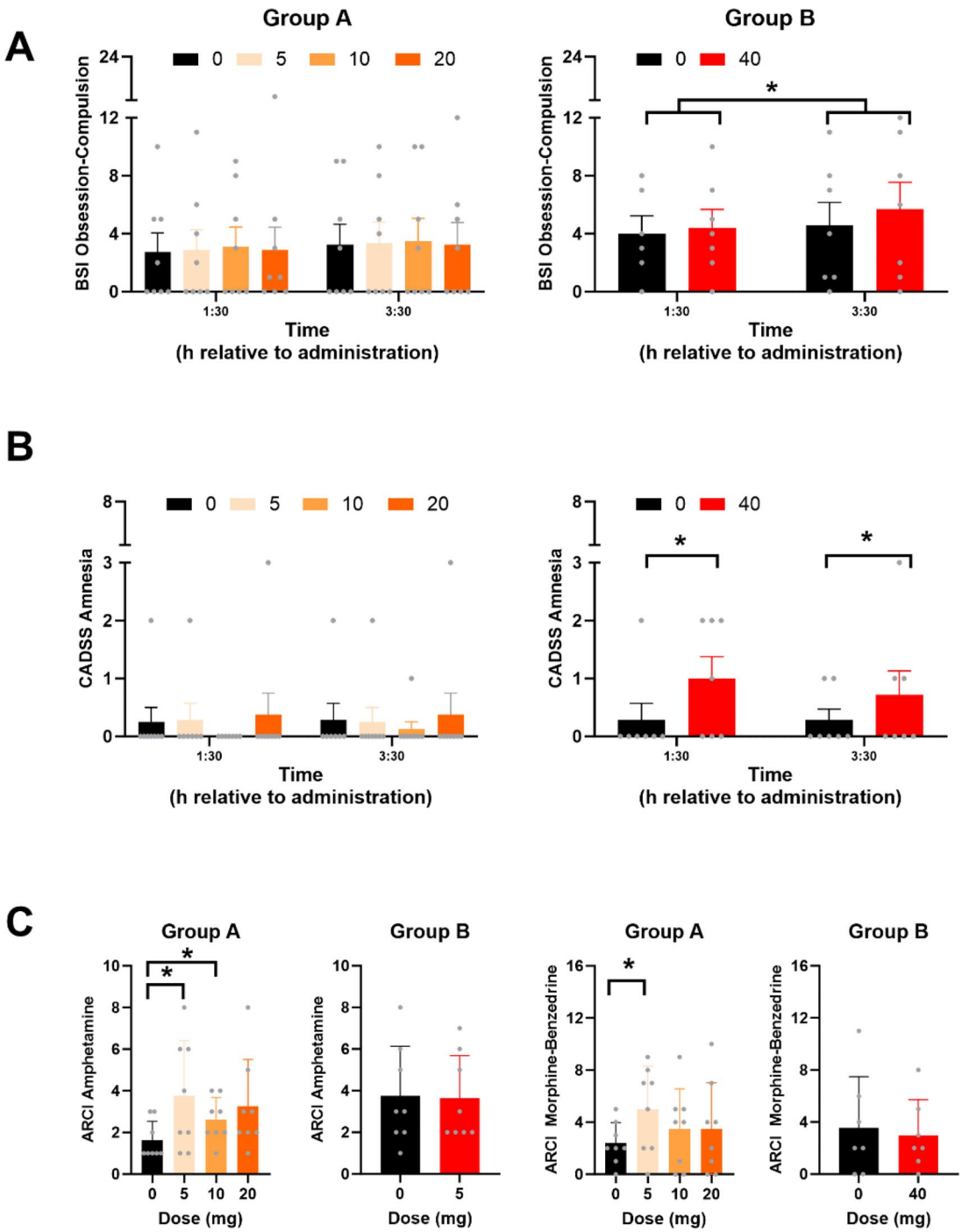

Fig. 2 Mean (SE) values for (BSI) Obsession-Compulsion subscale (**A**), CADSS amnesia (**B**), ARCI Amphetamine and Morphine Benzedrine Group (**C**) scales as a function of treatment and time after administration in both parts of the study. The ARCI ratings were taken at 1 h after drug. BSI: Brief Symptoms Inventory; CADSS: Clinician-Administered Dissociative State Scale; ARCI: Addiction Research Center Inventory

contrasts also revealed no significant differences (for statistics, see Tables S4-S5).

Neurocognitive performance

GLM analyses (Drug or Drug by Time) showed no main effects on the performance scores of the DSST, SCWT, PMT, MFFT, PVT, and SST in both parts of the study, with the exception only for the number of attentional lapses in the PVT ($F_{3,21}$=4.222, p=.017, ηp^2=0.376) in part A. Moreover, neither drug-placebo contrast analyses revealed significant effects on the performance scores of all these tasks, except for PVT and SST. Drug-placebo contrasts showed that mitragynine 5 mg significantly reduced the number of attentional lapses in the PVT ($F_{1,7}$=8.209, p=.024, ηp^2=0.540) but increased the number of errors in SST ($F_{1,7}$=6.760, p=.035, ηp^2=0.491).

Mean (SE) values for some of the major neurocognitive measures in each treatment condition as a function of time after drug administration, are shown in Figs. 3 and 4. Associated statistics, and those for additional neurocognitive parameters, are presented in Tables S4-S5.

Pharmacokinetics

The results of the mitragynine blood concentrations in part A showed that mitragynine doses produced a peak concentration of about 5.7, 15.7, and 25.6 ng/mL after 1 h. PK findings were compatible with two other pharmacokinetic studies on healthy kratom users (Tanna et al. 2022; Trakulsrichai et al. 2015), that found mitragynine following a two-compartmental model after oral intake. See Fig. 5 for mean (SE) concentrations of mitragynine in part A.

Discussion

The present study aimed to evaluate the safety (i.e. vital signs and adverse events) and impact on neurocognitive performance of single acute doses of mitragynine. Mitragynine did not have a significant effect on the majority of outcome measures at any dosage level and was well-tolerated. Still, the lowest dose (5 mg) increased subjective ratings of amphetamine-like arousal and attention. Further, the 5 mg dose increased accuracy in a sustained attention task and increased errors in the stop-signal task as compared to placebo. The highest dose (40 mg) of mitragynine increased subjective ratings of amnesia and produced some mild symptoms of psychological distress. Moreover, vital signs were not significantly affected by mitragynine, and only mild, transient side effects were reported.

In our study, mitragynine doses between 10 and 40 mg caused a slight decrease in blood pressure and respiratory rate. These variations were within the normal range, and therefore not considered clinically relevant. Such findings contrast with cardiorespiratory toxicities described in the literature (Brogdon et al. 2022; Sheikh et al. 2021) and cardiological alterations, including sinus tachycardia (Leong Abdullah et al. 2021), prolonged QTc interval (Leong Bin Abdullah and Singh 2021), and increased blood pressure/pulse rate in regular kratom users after drinking kratom tea containing up to 20 mg of mitragynine (Trakulsrichai et al. 2015). This suggests that the cardiovascular effects of mitragynine might be different in chronic kratom users who use higher doses or products containing other substances/contaminants, often considered responsible for health hazards. At the same time, lab safety data (clinical chemistry, hematology, and urinalysis) in the present study did not show significant deviations from normal ranges. These results are in line with findings showing that kratom did not cause alterations in blood exams of kratom users (La-Up et al. 2021, 2022; Ramachandram and Sangarran Chia Siang 2023; Singh et al. 2018; Vicknasingam et al. 2020). Further, no significant adverse events were described and only mild, transient side effects (e.g., dizziness, headache, sleepiness) were reported from participants which were related to the highest (40 mg) dose of mitragynine. In the literature (Cinosi et al. 2015; Grundmann 2017; Grundmann et al. 2023; Kruegel and Grundmann 2018), these adverse events have been reported and are often linked to chronic use. However, they did not have any clinical relevance and resolved spontaneously without treatment.

We also found that the lowest dose (5 mg) of mitragynine increased subjective ratings of amphetamine-like arousal, subjective feelings of attention, improved accuracy in a sustained attention task and decreased inhibition in the stop signal task. Additionally, amphetamine-like arousal was also increased by mitragynine 10 mg. Such findings would suggest that low doses of mitragynine exert stimulant effects. Further, mitragynine might increase euphoria, as shown by the ratings in the Morphine Benzedrine Group scale, and selectively ameliorate cognitive performance. Increments in euphoria as assessed with the ARCI rating scale have been reported before in daily kratom users (Smith et al. 2024b). Taken together, these results suggest that mitragynine might induce some stimulatory effects on attention and arousal, supporting some previous claims that kratom products can enhance cognition (Cinosi et al. 2015; Prevete et al. 2021; Swogger et al. 2022). These data are also in line with reports from kratom users claiming that kratom does not cause cognitive impairment (Singh et al. 2019b).

Mitragynine also exhibited stimulant effects at higher doses, as a single dose of 40 mg also led to an increase in

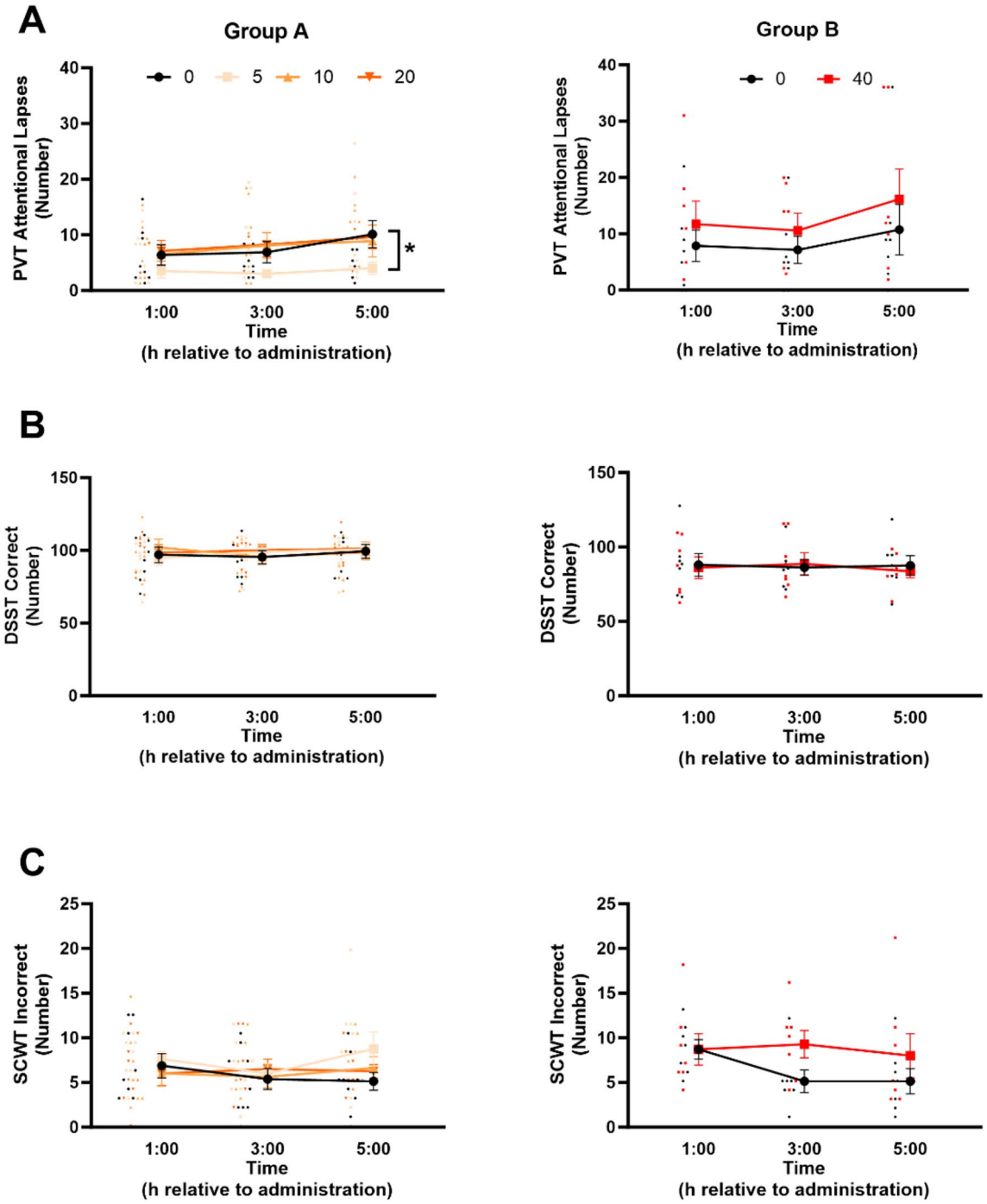

Fig. 3 Mean (SE) values for PVT (**A**), DSST (**B**), and SCWT (**C**) as a function of time after drug administration in both parts of the study. PVT: Psychomotor Vigilance Task; DSST: Digit-Symbol Substitution Task; SCWT: Stroop Color and Word Test

subjective ratings of impulsivity symptoms. However, the 40 mg dose of mitragynine also increased subjective ratings of amnesia and symptoms of obsessive-compulsive behaviour, suggesting a potential sedative effect on cognition and a potential to induce symptoms of psychological distress. Overall, the stimulant and inhibitory effects of mitragynine shown in our study support earlier claims of kratom's double action, which has been described as psychostimulant at low doses, and sedative at high doses (Kruegel and Grundmann 2018; Prozialeck et al. 2012; Singh et al. 2019b; Swogger et al. 2022) or both (Peran et al. 2023; Smith et al. 2023a).

Preclinical evidence suggests that kratom alkaloids might produce stimulant effects and enhance mood through adrenergic, opioidergic, and serotonergic receptors (Johnson et

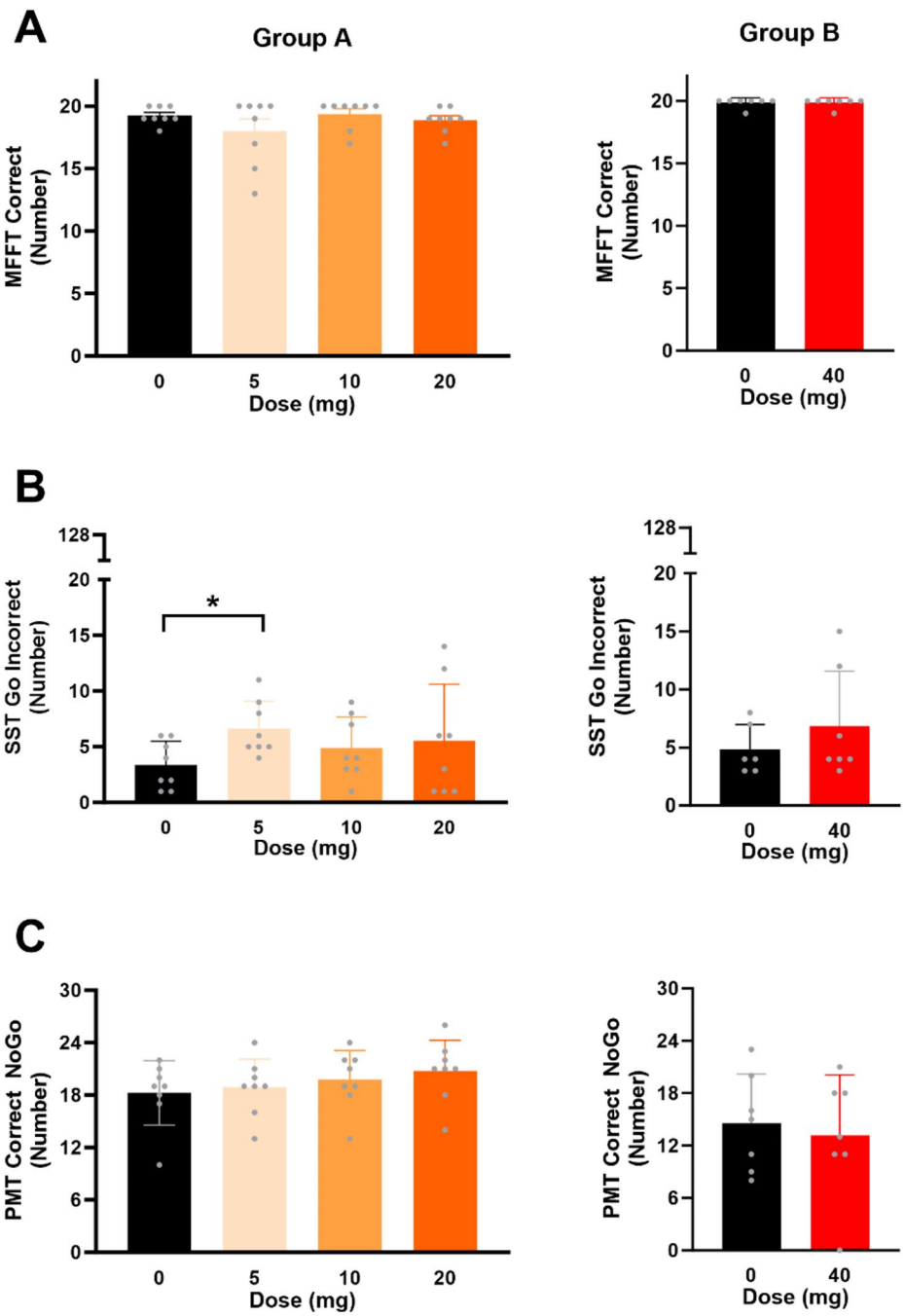

Fig. 4 Mean (SE) values for MFFT, SST, and PMT as a function of time after drug administration in both parts of the study. MMFT and SST were conducted at 1 h after drug administration. The PMT was conducted at 2 h after drug. MMFT: Matching Familiar Figures Test; SST: Stop-Signal Task; PMT: Prospective Memory Task

al. 2020; León et al. 2021; Obeng et al. 2021, 2022; Smith et al. 2023a). These systems could potentially explain the low-dose stimulatory effects in our study, but exactly how is unclear. Conversely, high doses of mitragynine in preclinical models may impair cognition and memory through cortical neural activity changes (Thériault et al. 2020) and interference with hippocampal synaptic transmission through long-term potentiation and Ca2 + influx inhibition (Hassan et al. 2019). Mitragynine has a strong affinity for the 5-HT1A receptor where it acts as a partial agonist (McCurdy et al. 2024). Stimulation of 5-HT1A receptors have been shown to interfere with memory-encoding mechanisms (Ogren et al. 2008). These mechanisms may potentially explain the impairing effects of mitragynine 40 mg on memory, but further research is needed to fully understand the behavioral pharmacology of mitragynine.

Finally, no significant effects on pain endurance were found in our study, despite preclinical data, several anecdotal reports (Chin and Mark-Lee 2018; McCurdy et al. 2024; Prevete et al. 2023; Swogger et al. 2022), and an RCT (Vicknasingam et al. 2020) suggesting the analgesic potential of kratom and mitragynine. Mitragynine concentrations

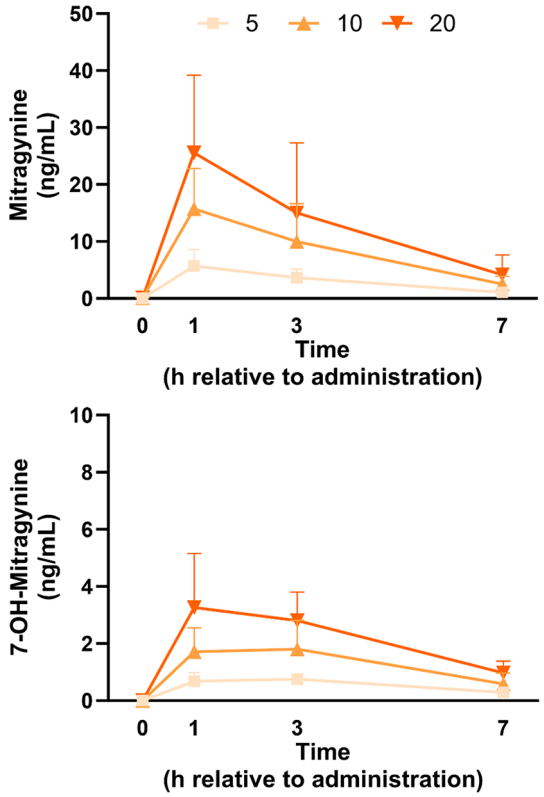

Fig. 5 Mean (SD) of mitragynine and 7-OH-mitragynine concentrations at baseline and at 1, 3, and 7 h after administration. Due to technical issues, data from Group B was missing

were comparable to those assessed in a controlled study with dried kratom leaf powder containing mitragynine doses that were comparable to those in the present study (Huestis et al. 2024). This suggests that mitragynine doses in the present study were well absorbed. Still, the absence of any analgesic effect might be related to the low dose range in the present study. In the only published RCT to date in which analgesic effects of a kratom decoction drink were observed in daily kratom users, mitragynine concentrations rose by 500–1000 ng/nl after a single drink (Vicknasingam et al. 2020). In the present study, mitragynine concentrations after 20 mg increased by about 30 ng/ml and from that it could be projected that the 40 mg dose increase mean mitragynine concentrations by about 60 ng/ml. Even though the present study utilized healthy volunteers that were naive to kratom use and did not develop kratom tolerance, the present doses might still have been too low to observe any analgesic effects.

This study has some limitations. First, this was an exploratory study in which the dose was chosen based on limited information from a previous studies with kratom. The dose range might be (much) lower compared to estimated daily use in regular kratom users. Furthermore, our findings are preliminary and come from a small sample of fifteen subjects. Thus, further investigations with higher mitragynine doses, larger sample sizes and full PK analyses are warranted. It should also be noted that we did not collect any ECG post dosing. Previous reports have indicated tachycardia with (Leong Bin Abdullah and Singh 2021) and without (Leong Abdullah et al. 2021) prolongated QTc intervals in kratom users. Therefore, more research will be needed to fully understand the cardiovascular effects of mitragynine, also at low doses.

In summary, the present study suggests that doses of mitragynine ranging between 5 and 40 mg were well tolerated in a controlled setting and that low doses (5–10 mg) of mitragynine may cause subjective feelings of stimulation and increased attention, pointing in the direction of enhancement of performance. On the other side, the highest dose (40 mg) might also produce inhibitory effects resulting in amnesia and psychopathological distress.

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Author contributions EP: Conceptualization, Data analyses, Writing-Draft, Review & Editing; ELT: Conceptualization, Review & Editing; KPCK: Conceptualization, Review & Editing; RP: Medical supervision and screening, Review & Editing; JTR: Logistics, Data collection, Data Curation, Review & Editing; MC: Data Collection, Data Curation, Review & Editing; SWT: PK analysis, Review & Editing; SR: PK analysis, Review & Editing; GB: Review & Editing; OC: Review & Editing; MP: Review & Editing; JGR: Funding, Conceptualization, Data Analysis, Writing, Review & Editing and Supervision. All authors approved the final version of the manuscript.

Declarations

Conflict of interest None.

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