A pilot, placebo controlled, dose-finding, pharmacodynamic and pharmacokinetic study of orally administered botanical kratom in non-dependent, recreational polydrug users with opioid experience under fed conditions

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Abstract

FDA has warned consumers about kratom (*Mitragyna speciosa*), a plant endogenous to Southeast Asia containing alkaloids with affinity and activity at mu opioid receptors, sites known to be associated with abuse potential. Although kratom use is prevalent in the US, prospective clinical investigations have been limited. This pilot study evaluated the pharmacodynamic (PD) effects, safety, and pharmacokinetics (PK) of the kratom alkaloids: mitragynine, 7-hydroxymitragynine (7-HMG), paynantheine, speciogynine, and speciociliatine following oral administration of botanical kratom.

Introduction

Kratom is a member of the coffee family (Rubiaceae) and native to countries in Southeast Asia, including Thailand, Malaysia, New Guinea, and the Philippines. For centuries, the leaves of the kratom plant have been used for cultural, recreational, health-promoting, and medicinal purposes. Fresh kratom leaves are usually chewed or made into tea for use. Products prepared from kratom leaves are available through the Internet and via brick-and-mortar stores. According to the National Survey on Drug Use and Health, an estimated 1.7 million Americans aged 12 and older used kratom in 2021[1]. In addition, kratom-related exposures reported to poison control center increased from 2014-2019[2].

FDA has determined that kratom is not appropriate for use as a dietary supplement and has concluded that kratom is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury[3]. Kratom is a botanical product that contains a mixture of indole-based alkaloid compounds. At least 25 alkaloids have been isolated from kratom; mitragynine represents about 66% of the total extractable alkaloid content of kratom, with paynantheine, speciogynine, and 7-hydroxymitragynine being the next most abundant[4]. In vitro binding studies have demonstrated that mitragynine and 7-hydroxymitragynine (7-HMG) bind to μ opioid receptors and that mitragynine has pharmacological activity at a variety of receptors including other opioid (i.e., κ and σ), serotonergic, and adrenergic receptor subtypes[5]. 7-HMG may be the most potent of the alkaloids with regard to psychoactive effects and is self-administered by animals whereas mitragynine is not[6]. Thus, while mitragynine and 7-HMG are thought to mediate most of kratom's pharmacologic effects, the presence of other minor alkaloid compounds such as speciociliatine may contribute to the overall effect of kratom through multiple pharmacologic pathways.

While there are extensive anecdotal reports regarding the use of kratom in the US, Malaysia, and Thailand, overall, the available clinical literature is sparse. Most published studies on kratom are not controlled or prospective, utilize varied kratom products, and there are few studies directly correlating specific doses of kratom with study endpoints. Within the case reports available, many describe subjects that had a history of chronic kratom use, consumed large amounts of kratom, and/or used multiple substances. Other studies reported in the literature are retrospective analyses of poison center databases, case studies, autopsies, and social media posts, as well as survey (self reported information) and interview (conducted by trained professional) studies. There are only a few prospective clinical pharmacokinetic studies. Because of the dearth of properly controlled clinical investigations, the current study proposed to examine the pharmacokinetics and pharmacodynamic effects of botanical kratom. These data may be useful to help characterize the safety of kratom and inform future investigations of its pharmacological effects.

Materials and Methods

This study was performed under an Investigational New Drug (IND) application. Botanical kratom was obtained from Sun Distribution, Super Organics. 40 healthy recreational polydrug users (8 subjects/cohort; 6 active:2 placebo) completed the study. To be included in the study, subjects had to have experience with opioids, defined as recreational use ≥10 times in their lifetime and ≥ one time in the past 12 weeks. In addition, subjects had to have used ≥ two or more perception altering drugs or stimulants on ≥ five occasions in their lifetime. Subjects were otherwise healthy with exclusions for significant diseases and a history of substance use disorder.

This study utilized a between-subjects design where subjects randomly received a single dose of placebo or kratom. The planned starting dose was 1g and subsequent doses of 3, 8, 10, and 12g were administered after interim safety and pharmacodynamic (PD) data reviews following the completion of each cohort. Once enrolled, subjects received orally administered kratom (made up of 500 mg/capsule) or placebo under double blind conditions. Subjects arrived at the research unit the day before dosing and study capsules were administered under fed conditions after a standardized high fat meal. After dosing, serial assessments of pharmacodynamic (PD) subjective effects using Visual Analog Scales (VAS) and blood samples were collected over 24 and 48 hours, respectively. Safety and tolerability were assessed throughout the study and subjects left the research unit 48 hours after doing. Safety assessments included AE monitoring, laboratory tests, vital signs (blood pressure, pulse, respiratory rate, oxygen saturation, and body temperature), ECG assessments, physical examination findings, and C-SSRS.

A validated UHPLC method using MS/MS detection was employed in determining sample concentrations of the kratom alkaloids in human plasma. Additional analyses of alkaloids are forthcoming.

Results

Forty subjects (N=40) completed the study, with N=8 subjects/cohort. The composition of the botanical kratom appears in Table 1.

Alkaloid	Capsule Content (mg)
Mitragynine	5.07 ± 0.71
Speciogynine	0.92 ± 0.13
Speciociliatine	1.98 ± 0.26
Mitraciliatine	0.29 ± 0.04
7-Hydroxymitragynine	BLLQ*
Paynantheine	1.28 ± 0.18
Corynantheidine	0.13 ± 0.02
Corynoxine A	0.04 ± 0.01
Corynoxine B	BLLQ*
Mitraphylline	BLLQ*
*BLLQ = below the limit of quantification (1 ng/mL equivalent to 32 ng/capsule	

Table 1. Alkaloid content of botanical kratom. Values represent alkaloid quantities per capsule administered.

No deaths or serious adverse events (SAEs) occurred. An SAE was defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions), is a congenital anomaly or birth defect, is an important medical event (including development of drug dependence or drug abuse) that may jeopardize the subject or require intervention to prevent one of the other outcomes listed above (according to medical judgment of an Investigator). In addition, no stopping criteria were reached, defined as one kratom-related SAE occurring in a cohort or moderate or severe AEs in 50% or more subjects in a cohort. AEs by System Organ Class (SOC) when total kratom events reported were greater than placebo appear below in in Table 2.

SOC [n(%)]	Kratom 1 g (N=6)	Kratom 3 g (N=6)	Kratom 8 g (N=6)	Kratom 10 g (N=6)	Kratom 12 g (N=6)	Pooled Placebo (N=10)	Pooled kratom (N=30)
Gastrointestinal Disorders	0	0	2 (33.3%)	1 (16.7%)	2 (33.3%)	2 (20%)	5 (16.7%)
Nervous System Disorders	1 (16.7%)	0	1 (16.7%)	3 (50%)	0	6 (60%)	5 (16.7%)
Psychiatric Disorders	0	0	1 (16.7%)	2 (33.3%)	0	1 (10%)	3 (10.0%)
Skin and Subcutaneous Disorders	1 (16.7%)	0	0	0	1 (16.7%)	0	2 (6.7%)
General Disorders	0	0	0	1 (16.7%)	1 (16.7%)	0	2 (6.7%)

Table 2. Adverse events by SOC.

When examining AEs by preferred term (PT), vomiting was the most common adverse event (AE) reported, with a total of five reports. Events by PT when total kratom frequency was greater than placebo *and* greater than one event appear below in Table 3.

Preferred Term [n(%)]	Kratom 1 g (N=6)	Kratom 3 g (N=6)	Kratom 8 g (N=6)	Kratom 10 g (N=6)	Kratom 12 g (N=6)	Pooled Placebo (N=10)	Pooled kratom (N=30)
Vomiting	0	0	2 (33.3%)	1 (16.7%)	2 (33.3%)	0 (0%)	5 (16.7%)

Table 3. Adverse events by preferred term.

Preliminary assessments of kratom alkaloid exposure(s) suggested orderly, dose-related effects. Mitragynine exposure increased as a function of dose. Analysis of plasma concentrations suggested a variable Tmax that occurred between 2 and 4 hours. Time course data for mitragynine appear below in Figure 1. Analyses of additional alkaloids are pending.

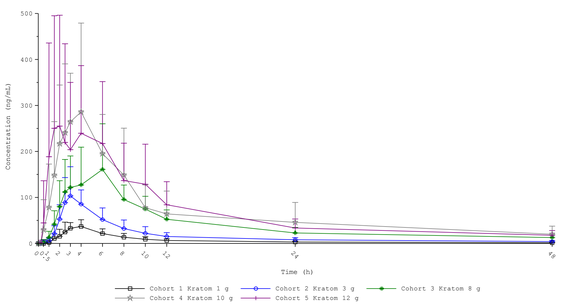

Figure 1. Mean (+SE) plasma concentration-time profile of mitragynine following oral administration of botanical kratom

At doses > 1g Kratom appeared to produce mild pupillary constriction. This pupillary constriction appeared to have a dose-related component with maximum levels of occurring at doses ≥3g. At all doses, pupil constriction was time dependent and resolved 12 h after dosing (Figure 2). Maximum, mean constriction was 2.42 mm after 12g.

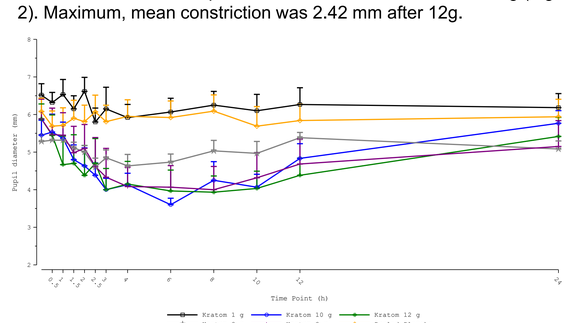

Figure 2. Mean (+SE) for pupil diameter measurements over time following a single, oral administration of botanical kratom

No dose-related effects were observed on numerous study endpoints assessing the subjective profile of botanical kratom. For example, on measures of at the moment drug liking, kratom produced minor increases from baseline with substantial overlap and no apparent dose-response. The 8 and 12g doses appeared to produce the largest changes, although they did not appear to be significantly different from placebo (Figure 3).

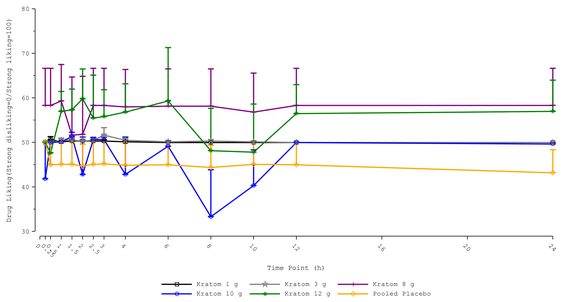

Figure 3. Mean (+SE) VAS measures of drug liking over time following oral kratom administration

Similarly, when examining maximum ratings (Emax) of VAS assessments of overall drug liking and take drug again 12 and 24 hrs after dosing, no apparent dose-related effects were observed following administration of kratom capsules (Figure 4).

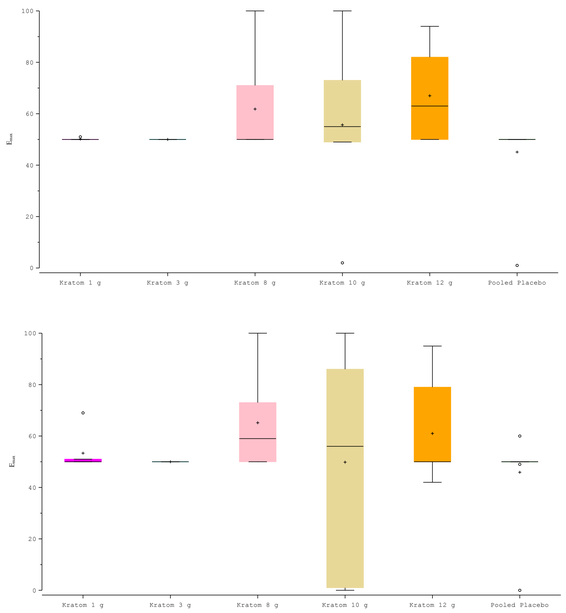

Figure 4. Box-and-Whiskers plot for maximum (Emax) ratings of overall drug liking (top) and take drug again (bottom)

However, kratom appeared to produce dose-related effects on a variety of subjective measures assessed as non-key secondary endpoints. For example, mean ratings of "high" (33.7) and "feeling drunk" (15.7) were highest at the maximum (12 g) dose of kratom. These effects appeared to have resolved by 8 hour timepoint (Figure 5).

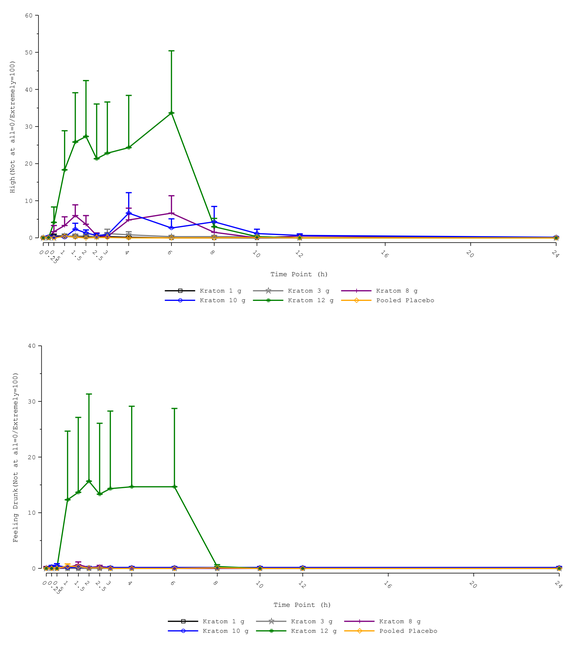

Figure 5. Mean (+SE) VAS ratings of feeling high (top panel) and feeling drunk (bottom panel) over time following oral administration of kratom

Discussion

Preliminary data are shown for this pilot, single ascending dose-response (SAD) study of botanical kratom. At the doses tested (1, 3, 8, 10, and 12g), no serious adverse events (SAEs) occurred. Vomiting was the most common AE and showed an increased trend in the higher dose range (i.e., 8, 10, and 12g) compared to the lower doses. Overall, the data suggest that at the doses tested, using the specific botanical kratom sourced for the study, and under carefully controlled clinical conditions (i.e., an inpatient study), kratom was well-tolerated. These data help inform the safety profile of botanical kratom for use in future investigations to more thoroughly characterize its pharmacological effects and abuse potential.

It is unclear how the single sourced, botanical kratom used in our study compares to the wide array of kratom-related products available on the marketplace. Though data are limited, the mitragynine and 7-HMG content of the kratom used in our study is consistent with that reported in the literature. However, more than 50 alkaloids exist in the kratom plant that may have pharmacological effects. Importantly, there is a growing trend of newly created kratom "extracts" that have enriched and increased levels of kratom alkaloids, including increased levels of mitragynine and 7-HMG[7]. For example, a recent investigation of commercially available kratom products found "pressed pills" purportedly derived from kratom with 7-HMG levels far greater than those in naturally occurring (i.e., botanical) kratom[8]. It is unclear how these high levels of 7-HMG were achieved given the low levels of 7-HMG in naturally occurring kratom. However, the high 7-HMG concentrations may be achieved via chemical conversion of mitragynine to 7-HMG, resulting these semi-synthetic kratom products.

Initial assessments of the pharmacokinetic (PK) profile of the kratom alkaloids suggested orderly dose-effects. Maximum plasma levels (i.e., Cmax values) of mitragynine ranged from 250-300 ng/mL. Notably, Cmax values following 12g appeared to be greater than those after the 10g dose, suggesting dose-related PK effects. These data add to the existing kratom literature, as to our knowledge the 12g dose of kratom administered in this study is the highest dose reported in the literature to date. Additional analyses of 7-HMG and other kratom alkaloids are forthcoming.

Kratom produced pupillary constriction, a finding consistent with mu-opioid effects. However, this constriction was relatively mild (~2 mm maximal constriction), compared to other opioids such as morphine and oxycodone that have been show to produce >4 mm of pupillary constriction at high doses[9,10]. Nonetheless, these data appear consistent with the pharmacological effects of mitragynine which has been shown to have affinity and activity at mu-opioid receptors, a finding consistent with the antinociceptive effects produced by kratom[11].

Kratom did not appear to produce clear, dose-related or significant effects on VAS-rated measures commonly associated with abuse potential including ratings of drug liking, overall drug liking, and assessments of take drug again. However, kratom did produce a constellation of effects commonly associated with drugs of abuse such as increases in subject-rated measures of good effects, high, and feeling drunk. These data warrant additional studies to more thoroughly assess the abuse potential of kratom.

Conclusions

- This was a pilot, proof-of concept study investigating the safety of single sourced botanical kratom. It did not have detectable 7-HMG levels found in some marketed kratom products, thus, the results might not be representative of drug effects associated with other kratom-containing products in the marketplace.
- The small sample size limits the interpretability and translatability of the data.
- This study was not a formal HAP assessment and there are methodological differences between this SAD and HAP studies. For example, a within-subjects design was not used and no qualification session preceded study subject enrollment into the study. In addition, there was no positive control administered for comparative purposes.
- This study utilized encapsulated, ground kratom leaf powder. It is unknown how the results of this study may extend to other kratom preparations such as teas that are commonly used to ingest kratom and may result in increased alkaloid dissolution and bioavailability. This may be significant, as the volume of kratom administered was relatively large (e.g., at the maximum dose, subjects ingested 24 size 00 capsules).
- Future studies more thoroughly examining the abuse potential of kratom and its associated alkaloids may be warranted.

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