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A preliminary assessment of heavy metal (Pb, Cd, and As) contamination in the leaves and cultivation area of *Mitragyna speciosa* (Korth.) originating from Thailand

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Abstract

Kratom (*Mitragyna speciosa* (Korth.)) is a plant with various therapeutic applications, treating such ailments as chronic pain and diabetes. Its primary alkaloid, mitragynine, exhibits opioid-like effects without respiratory depression; thus, kratom may be used to treat opioid addiction. However, heavy metal contamination can compromise kratom's safety and quality. This study examined heavy metal contamination (from arsenic [As], cadmium [Cd], and lead [Pb]) in Thai kratom cultivation areas and dried leaves using inductively coupled plasma mass spectrometry (ICP-MS). Mitragynine concentrations in green Thai kratom (GTK) and red Thai kratom (RTK) were also quantified. The analysis revealed that the As, Pb, and Cr levels in kratom leaves were below the safety thresholds, but soil samples showed significantly high As contamination (177.94±1.30 mg/kg). Mitragynine concentrations were higher in GTK (52.68 mg/g $_{\text{(Ethanol extract)}}$) compared with RTK (39.77 mg/g $_{\text{(Ethanol extract)}}$). The findings provide essential information on heavy metal contamination and mitragynine content in kratom leaves and cultivation areas. While safe levels of heavy metals were found in leaves, elevated As concentrations in soil samples raise concerns about long-term contamination risks. The mitragynine content variability between GTK and RTK warrants further investigation to understand its pharmacological and therapeutic implications. This study emphasizes the need for continued kratom research to ensure kratom's safe and effective use in traditional and modern medicine.

Keywords: Kratom (*Mitragyna speciosa*), Heavy metal contamination, Mitragynine, Inductively coupled plasma mass spectrometry (ICP-MS)

1. Introduction

Kratom (*Mitragyna speciosa* (Korth.)) has been widely used for its traditional therapeutic benefits to address a range of health concerns, such as diarrhea, chronic pain, and diabetes [1]. Mitragynine, the primary alkaloid component in kratom, has been shown to produce opioid-like effects, including analgesia [2]. However, the efficacy of mitragynine is lower than that of morphine, and it offers additional benefits over morphine, such as the absence of respiratory depression and potential use in treating opioid addiction [3]. Owing to these advantages, kratom was declassified from the Narcotics Type 5 list on August 24, 2021. Following this change, Surat Thani province received authorization to cultivate high-quality kratom in an effort to promote kratom's use as an economically viable medicinal plant [4].

It has been reported in the Nampu subdistrict area that regular consumers of kratom show a significant reduction in triglycerides and low-density lipoprotein (LDL), as well as increased levels of high-density lipoprotein (HDL) compared with non-consumers [5]. Therefore, these findings might contribute to our overall understanding of kratom's effects, as well as potential implications for future research into traditional medicines for anti-obesity treatment. According to the standards set forth in the *Thai Herbal Pharmacopoeia* [6], traditional medicines must meet certain criteria to be registered. One criterion is that the medicine must not contain heavy metal contaminants, such as arsenic (As), cadmium (Cd), or lead (Pb). Specifically, the allowable concentrations in traditional medicines are less than 4 mg/kg for arsenic, less than 0.3 mg/kg for cadmium, and less than 10 mg/kg for lead. These standards are in place to ensure the safety and efficacy of traditional medicines and to prevent exposure to harmful heavy metals, which can have serious health implications [6].

Heavy metals are naturally occurring elements that are essential for life and play important roles in various biological processes. For example, iron (Fe) is a key component of hemoglobin, and zinc (Zn) is crucial for the functioning of over 300 enzymes in the human body [7]. However, these metals can become toxic when present in excessive amounts. Human activities, such as industrial and agricultural processes, contribute to increased heavy metal contamination in the environment [7]. Heavy metals, such as arsenic (As), cadmium (Cd), and lead (Pb), commonly contaminate soil, posing hazards to both the environment and human health. Exposure to lead (Pb) has been linked to various health problems, including poor muscle coordination, brain and kidney damage, reproductive abnormalities, slowed cognitive development, and learning deficits [8]. Similarly, arsenic (As) exposure has been associated with reduced productions of hemoglobin and red and white blood cells, as well as hypertension, diabetes, and neurodegenerative disorders [8]. Cadmium (Cd) exposure has been reported to cause irreversible renal tract damage, severe harm to the liver and lungs, and weakened bones [8]. Furthermore, co-exposure to Pb and Cd has been correlated with increased risks of diabetes and kidney dysfunction [9].

Soil concentrations of heavy metals can result from both natural factors, such as soil properties and mineral composition, and human activities, such as the use of chemical pesticides and fertilizers in cultivation. Heavy metal contamination in soil represents a significant environmental hazard because of the persistence, slow decomposition, and high toxicity of these metals. Moreover, heavy metals can accumulate in various parts of plants, and they can be transferred to humans through the food chain via soil-plant-human transmission [10]. The consumption of plants containing accumulated heavy metals can be toxic and detrimental to human cells and tissues, affecting overall health. In a previous report, heavy metals, including Mn, Cu, Cd, Pb, Fe, and Zn, were found in all traditional Chinese herbal medicine samples; except for Mn (18.54 mg/L), they were generally found in low concentrations (<1 mg/L) [11]. In addition, a study following *Chinese Pharmacopoeia* guidelines discovered that 30.51% of the examined samples contained at least one heavy metal exceeding permissible levels. The exposure assessment identified 25 herbal varieties with elevated risks related to Pb, Cd, As, and Hg. These 25 herbs present considerable health risks based on the Hazard Quotient or Hazard Index evaluation [12]. Moreover, lead (Pb) content in Ayurvedic medicine has been mentioned in the discussion of heavy metal contamination in traditional medicine [14]. Therefore, the contamination of herbal medicine with heavy metals remains a concern, and this highlights the need for rigorous quality control measures and regulations to ensure the purity and safety of traditional herbal medicines for public consumption.

This study aims to evaluate heavy metal contamination (e.g., from As, Cd, and Pb) in a kratom cultivation area and dried kratom leaves, using inductively coupled plasma mass spectrometry (ICP-MS). Moreover, it aims to develop a kratom plant control model via community participation in Thailand. The research is carried out via a case study of Nam Pu subdistrict, Ban Na San district, Surat Thani province. The assessment of contamination levels and potential health risks associated with heavy metals in kratom will serve as a basis for implementing recommended actions to eliminate heavy metal levels in herbal medicines. It will also facilitate the determination of levels of mitragynine, the major compound in kratom leaves.

2. Materials and methods

2.1 Soil sampling and processing

Kratom cultivation soil was collected from Developing a Kratom Plant Control Model by using community participation in Thailand: a case study of Nam Pu subdistrict, Ban Na San district, Surat Thani province (GPS: 8.7384933, 99.2657274; Latitude: 8° 38' 42.2" N; Longitude: 99° 53' 47.6" E). Soil samples were collected from three distinct orchards, with 15 random sampling points chosen within each orchard to ensure a representative sample from each site. The samples were extracted from a depth of approximately 15 cm, a common practice in soil science, as it encompasses the root zone where the majority of nutrient uptake occurs in most plants, including trees (Brevik et al., 2020) [15]. Following extraction, each sample was individually sealed in a plastic bag to prevent cross-contamination during transportation to the laboratory. Upon arrival, the soil samples were combined to create a homogeneous sample. This composite soil sample was then dried at 105°C for 24 h. Subsequently, 0.25 g of the sample, which had previously been sifted through a 2 mm sieve, was mixed with 1 mL of hydrogen peroxide, 2 mL of hydrochloric acid, and 9 mL of nitric acid in a Teflon container. The mixture was allowed to react for 5 minutes before the container was sealed. Next, the containers were placed in a vessel liner and heated at 180 °C for 5.5 minutes, maintained at that temperature for an additional 9.5 minutes, and then allowed to cool down before being diluted to 100 mL with deionized water.

2.2 Sample preparation of kratom leaf powder

In January 2022, Fresh kratom leaves were collected from three orchards located in the Nam Pu subdistrict. The kratom leaves were put in a sampling box, returned to the laboratory, and cleaned thoroughly with tap water. The leaves were spread out in a single layer on a tray or drying rack and placed in a hot air oven at 70°C for 48 h to ensure complete drying. After drying, the leaves were ground into a fine powder using a grinder, mortar, and pestle. The powder was passed through a fine-mesh sieve to remove any large particles that remained, resulting in a uniformly fine powder. Two grams of powder was mixed with 0.01 M with nitric acid (0.01 M HNO_3) for subsequent analysis using ICP-MS.

2.3 Detection of heavy metals with ICP-MS

All solution samples were analyzed using a Scientific X Series ICP-MS spectrometer (Perkin Elmer, NexION2000, USA). Heavy metal data obtained from ICP-MS were quantified using standard curves ranging from 0.5 to 15.0 mg/kg for Pb, Cd, and As elements. The limits of quantification (LOQs) achieved for the metals' contamination in soil were 2 mg/kg^{-1} for As, 4 mg/kg^{-1} for Cd, and 2 mg/kg^{-1} for Pb. Meanwhile, the LOQs achieved for metal contamination in the kratom leaves was 0.041 mg/kg^{-1} for As, 0.046 mg/kg^{-1} for Cd, and 0.083 mg/kg^{-1} for Pb.

2.4 Liquid chromatography analysis of mitragynine in kratom

The analysis employed a high-performance liquid chromatography (HPLC) system (Thermo Fisher Scientific, MA, USA). Prior to analysis, all samples were subjected to filtration using a nylon filter with a pore size of 0.22 µm. Separation of the analytes was achieved using a Thermo Hypersil GOLD C18 column (2.1 × 100 mm, 1.9 µm). The mobile phase consisted of a gradient mixture of solvent A (0.1% formic acid, pH 2.99) and solvent B (acetonitrile) at a flow rate of 0.5 mL/min. The gradient program employed was as follows: 0-5 min, 25% B; 6-15 min, 25-100% B; 15-25 min, 100% B; 25-26 min, 100-25% B; and 26-40 min, 25% B. The injection volume was set at 10 µL, and the detection wavelength was 254 nm. Standard compounds, including mitragynine (0-100 µg/mL) sourced from Lipomed, Inc. (lot number 1610.1B0.2), were employed as references in the analysis.

2.5 Statistical analysis

The results are presented as the average ± standard deviation based on three replicate measurements. For the statistical analyses, GraphPad Prism software, version 5 (GraphPad Software, San Diego, CA, USA), was employed.

3. Results

Per the *Thai Herbal Pharmacopoeia*, contamination of Thai kratom with the heavy metals arsenic (As), cadmium (Cd), and lead (Pb) should be limited to less than 4 mg/kg, 0.3 mg/kg, and 10 mg/kg, respectively. To assess the heavy metal concentrations in RTK and GTK collected from the cultivation area, we measured the levels of As, Cd, and Pb in dry powder. Our findings showed that the concentration values of 0.324 ± 0.17 mg/kg for As, 0.142 ± 0.28 mg/kg for Cd, and <0.083 mg/kg for Pb were detected in GTK, while concentrations of 0.513 ± 0.96 mg/kg for As, 0.147 ± 0.24 mg/kg for Cd, and <0.083 mg/kg for Pb were detected in RTK (Table 1). Based on these results, kratom leaves do not contain concentrations of Pb, As, or Cd that are above allowable limits based on the *Thai Herbal Pharmacopoeia*.

Subsequently, we investigated heavy metal contamination in the cultivation areas of kratom by analyzing soil samples collected from both GTK and RTK using the ICP-MS technique. Our results indicated that the levels of Pb and Cd contamination in the soil were below the recommended standards set by the *Thai Herbal Pharmacopoeia*. However, the level of As contamination was significantly higher than the standard limit of 6 mg/kg, with a concentration of 177.94 mg/kg; this exceeded the recommended limit by 30 times (Table 1).

Subsequently, we quantified the amount of mitragynine, the primary bioactive compound, in both GTK and RTK. To extract the compound, 10 g of dry powder was soaked in 100 mL of 95% ethanol for 24 hours. After the ethanol was removed, we obtained 1 g of crude ethanol; of this, 10 µg of crude ethanol was subjected to HPLC analysis using a C18 column as the separation. Mitragynine from GTK and RTK had concentrations of 52.68 ± 5.91 mg/g (Ethanol extract) and 39.77 ± 2.60 mg/g (Ethanol extract) (Figure 1), respectively, as compared with the mitragynine standard.

Table 1 Levels of As, Pb, and Cd contamination in green and red Thai kratom leaves and kratom cultivation area.

	Heavy metal (mg/kg)	
	Sample	Standard [6]
Green Thai Kratom		
Arsenic (As)	0.324 ± 0.17	<4
Cadmium (Cd)	0.142 ± 0.28	<0.3
Lead (Pb)	<0.083	<10
Red Thai Kratom		
Arsenic (As)	0.513 ± 0.96	<4
Cadmium (Cd)	0.147 ± 0.24	<0.3
Lead (Pb)	<0.083	<10
Kratom Cultivation Area		
Arsenic (As)	177.94 ± 1.305	<6
Cadmium (Cd)	<4	<67
Lead (Pb)	92.69 ± 0.31	<400

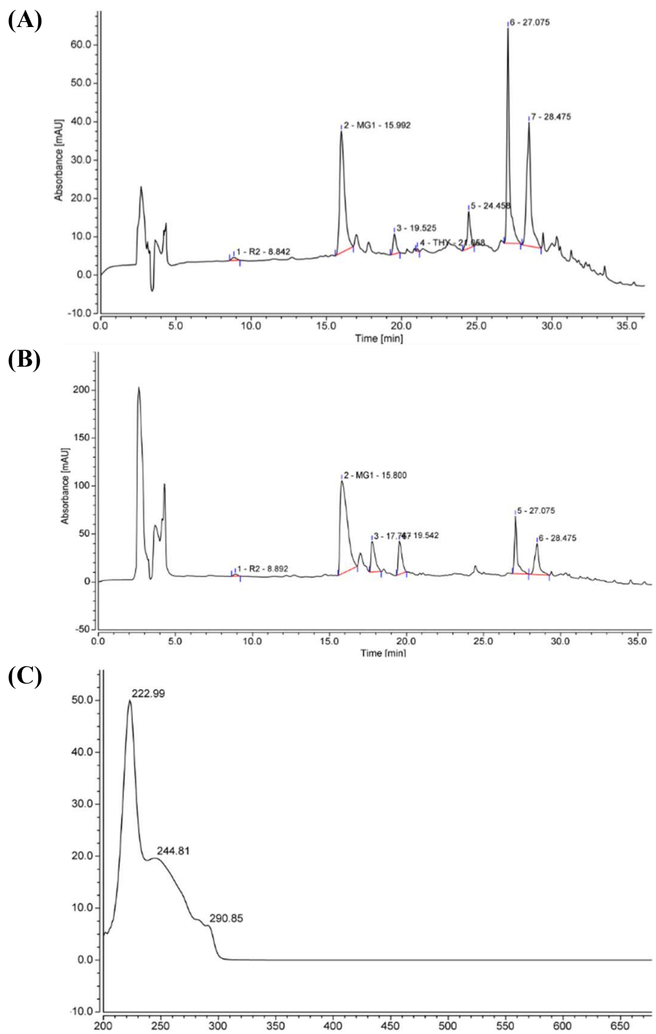

Figure 1 High-performance liquid chromatography analysis of mitragynine in red Thai kratom (A) and green Thai kratom (B). The analysis focused on the determination of mitragynine. Mitragynine, the target compound, exhibited an elution time of 15.5 minutes, as indicated by the absorption spectrum (C), compared with the mitragynine standard compound. The experiments were conducted with triplicate measurements for each sample, ensuring reliable and robust results.

4. Discussion

The experimental results demonstrate that both GTK and RTK exhibit lower levels of As, Pb, and Cd contamination compared with the established safety thresholds. However, soil samples collected from the kratom cultivation areas revealed elevated As concentrations, surpassing the standard levels by 30 times. This study presents the first evidence of As contamination in the soil of kratom cultivation sites occurring while the kratom leaves themselves exhibit no detectable levels of As. Potential sources of As contamination in the soil may include water sources, pesticide usage, and chemical fertilizers. Our findings align with previous research conducted in the southern region of Thailand, particularly in the Ron Phibun district, where higher As concentrations were detected in the urine of farmers from areas with elevated contamination levels compared with those from areas with lower contamination levels [13]. The same study identified a correlation between the use of groundwater in households and increased As concentrations in urine, raising significant public health concerns [13,14].

The observed lack of As contamination in kratom leaves, despite the high levels in the soil, could be attributed to several factors. These include a unique As absorption mechanism in kratom plants, the quality of irrigation water, and the detection limit of the analytical method used. Some plant species possess distinct absorption mechanisms, enabling them to absorb more As than others [15]. Kratom may have a mechanism that prevents As uptake from the soil. In addition, soil properties, such as pH and organic matter content, can influence As solubility, potentially leading to low As availability for kratom plants [16]. Further investigation is needed to identify specific sources of contamination and develop strategies for mitigating the associated risks, as well as to assess arsenic levels in the urine of people in kratom cultivation areas.

In this study, we quantified mitragynine, the primary bioactive compound in GTK and RTK, using an ethanol extraction method and HPLC analysis with a C18 column. We found mitragynine concentrations of 52.68 ± 5.91 mg/g in GTK and 39.77 ± 2.60 mg/g in RTK, indicating a higher concentration in GTK; this may influence the varying effects reported by users of these kratom varieties. Previous studies have reported a wide range of mitragynine concentrations in different kratom strains and locations. For example, a study by Hassan et al. (2013) reported mitragynine concentrations ranging from 12 to 21 mg/g in Malaysian kratom samples [17]. A study by Kumarnsit et al. (2007) found mitragynine concentrations of between 8 and 55 mg/g in Thai kratom samples [18]. Mitragynine content in kratom leaves can vary significantly depending on such factors as plant genetics, geographical location, and environmental conditions. With regard to environmental conditions, a study by Zhang (2020) demonstrated that the concentrations of speciogynine, corynantheidine, and mitragynine per leaf dry mass in *Mitragyna speciosa* (kratom) were positively influenced by the application of low to medium rates of fertilizer. This suggests that strategic nutrient management could potentially enhance the production of these selected alkaloids, likely by encouraging nitrogen allocation toward secondary metabolic pathways [22]. In addition, the cultivation of *Mitragyna speciosa* (kratom) under greenhouse shaded conditions led to increases of 40%, 35%, and 111% in the concentrations of mitragynine, paynantheine, and corynoxine per leaf dry mass, respectively, when compared with those cultivated under full-sun field conditions [23]. In addition to the observed variability in mitragynine levels across different environmental conditions, this study hypothesized that plant age may play a significant role in influencing mitragynine concentrations. It is important to further investigate and elucidate the impact of plant age on mitragynine content to gain a comprehensive understanding of this compound's production in kratom plants.

To summarize, our findings on the mitragynine concentrations in GTK and RTK are generally consistent with the existing literature, although the concentrations are at the higher end of the reported range [19]. Further research is needed to better understand the factors contributing to the variability in mitragynine content and the potential implications for the pharmacological effects and therapeutic applications of kratom.

5. Conclusion

This study evaluated heavy metal contamination in RTK and GTK, as well as their cultivation areas. We found that the levels of As, Pb, and Cd in the kratom leaves were within the established safety thresholds. However, soil samples showed significantly high levels of As contamination, necessitating further investigation to identify the sources and develop strategies to mitigate potential risks.

Our study provides crucial insights into the presence of heavy metals, particularly lead (Pb), in kratom leaves, although it has some limitations that deserve attention. One potential issue is the possible contamination of kratom leaf samples with Pb during the grinding phase. Pb is frequently found in the metal soldering of various tools, including grinders, and could be introduced into the samples, potentially skewing the observed Pb concentration. However, it is important to highlight that the detected Pb levels in our samples fell below the threshold values recommended by the *Thai Herbal Pharmacopoeia*. This suggests that, despite the legitimate concern about possible Pb contamination from processing equipment, the levels in the samples were still sufficiently low. Moreover, the levels of Pb detected in the kratom samples from Thailand appear to be significantly lower than those reported in previous studies conducted by Prozialeck [25] and the US FDA, wherein the kratom samples were sourced from Indonesia. This difference could be significant, suggesting that kratoms sourced from one country might present lower metal contamination than kratoms from other countries. Moreover, we quantified mitragynine concentrations in both GTK and RTK, with GTK displaying a higher concentration. This research contributed valuable information to the existing literature on heavy metal contamination and mitragynine content in kratom, emphasizing the need for additional research on factors affecting the variability in mitragynine content and the subsequent implications for the pharmacological effects and therapeutic applications of kratom.

6. Acknowledgements

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