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HPLC-PDA METHOD FOR THE QUANTIFICATION OF MITRAGYNINE IN FRESH KRATOM *(MITRAGYNA SPECIOSA)* LEAF

Norliana-Izzati MR[2], Lee CT[1], Fauziah A[1], Zunoliza A[1], Ling SK[1], Mohd-Hafidz-Hadi A[1], Ng KKS[1], Ng CH[1,*], Tnah LH[1], Ng CL[2], Goh H-H[2] & Lee SL[1]

[1]*Forest Research Institute Malaysia, 52109 Kepong, Selangor*
[2]*Institute of Systems Biology, Universiti Kebangsaan Malaysia, 43600 UKM Bangi, Selangor*

**chinhong@frim.gov.my*

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Kratom (*Mitragyna speciosa*) is a psychotropic tropical plant that is used as a traditional remedy in Southeast Asia. It has many medicinal properties and has great potential for clinical applications. Mitragynine and 7-hydroxymitragynine (7-OH) are the important pharmacologically active compounds found in kratom with mitragynine as the major alkaloid found in the leaf. We report the development and validation of a high-performance liquid chromatography-photodiode array method for the determination and quantification of mitragynine from *M. speciosa* fresh leaf extract. Fresh leaf samples were cryogenically ground and freeze-dried before methanol extraction. Gradient elution was conducted using acetonitrile and ammonium bicarbonate buffer (pH 9.5) at a flow rate of 1 mL min^{-1}. Chromatogram separation was achieved using Kinetex EVO C18 column in a duration of 25 min with MG eluted at 15.75 min. The calibration curves were in a linear relationship with determination coefficients (R^2) ≥ 0.99. Mitragynine quantification was calculated based on the calibration curve equation. The precision value (RSD) was less than 2% and accuracy range from 93%–100%. The values for limit of detection (LOD) and limit of quantification (LOQ) were 0.67 µg mL^{-1} and 1.51 µg mL^{-1}, respectively. This method has been validated and found suitable for the quantification of mitragynine in fresh leaf. We found that freeze-drying during sample preparation from fresh leaf yielded more reliable mitragynine quantification, compared with that of conventional oven-drying method.

Keywords: *Mitragyna speciosa*, medicinal plant, bioactive compounds, method validation, freeze-drying

INTRODUCTION

Mitragyna speciosa (Roxb.) Korth. (Rubiaceae), commonly known as Kratom, is a tropical plant native to Southeast Asia, mainly found in Malaysia and Thailand (Burkhill 1935). Traditionally, kratom leaf has been used by the local community as remedy to treat fever, chronic pain and muscle pain (Kruegel & Grundmann 2018). This unique psychotropic plant species is reported to harbor many medicinal properties such as mood enhancer, analgesic, antitussive and opioid-like effects (Kruegel et al. 2019).

The main pharmacologically active compounds in *M. speciosa* that can bind to opioid receptors are mitragynine (9-methoxy-coryantheidine, MG), the major alkaloid, and 7-hydroxymitragynine (7-OH), with the latter being significantly more potent (Kruegel et al. 2019). Metabolomics profiling of *M. speciosa* leaf using LC-ESI-TOF-MS supported the presence of mitragynine and other alkaloids such as 7-OH, mitragynaline and paynantheine (Veeramohan et al. 2018).

Due to the potential clinical applications of mitragynine as well as for detection purposes, various methods for its quantification have been reported, such as LC-Q-TOF-MS and DART-HRMS (Fowble & Musah 2019). Development of HPLC detection and quantification methods for kratom commercial products such as capsules, powder and beverages has also been reported (Kowalczuk et al. 2013, Mudge & Brown 2017). However, HPLC method for extract from fresh leaf sample of *M. speciosa* was rarely reported, with a few involving extractions after oven or air-

drying of ground leaf samples (Karunakaran et al. 2022a, Parthasarathy et al. 2013). Therefore, in this study, a precise and accurate HPLC-PDA method for the quantification of mitragynine content in fresh kratom leaf was developed, particularly for our ongoing study investigating the effect of abiotic stress on mitragynine biosynthesis.

MATERIALS AND METHODS

Chemicals and reagents

Mitragynine ($C_{23}H_{30}N_2O_4$), formula weight (FW) 398.50 g mol^{-1}, CAS 4098-40-2, > 93% purity in powder form was purchased from Lipomed AG (Arlesheim, Switzerland). Supelco® LiChrorosolv® Reag. Ph Eur methanol (CH_3OH), FW 32.04 g mol^{-1}, CAS 67-56-1, acetonitrile (CH_3CN), FW 41.05 g mol^{-1}, CAS 75-05-8 were acquired from Merck (Darmstadt, Germany) with gradient grade for liquid chromatography. Ammonium bicarbonate (CH_5NO_3) ReagentPlus®, FW 79.06 g mol^{-1}, CAS 1066-33-7, ≥ 99% purity was obtained from Sigma-Aldrich (Missouri, USA). EMSURE® ammonia solution 25% from Merck (Darmstadt, Germany) and ultrapure water purified by ELGA PURELAB® Classic (London, UK) were used to prepare 5 mM ammonium bicarbonate buffer at pH 9.5.

Plant material and sample preparation

Leaf samples of a *Mitragyna speciosa* plant in the Forest Research Institute Malaysia nursery were collected and immediately frozen in liquid nitrogen. This *M. speciosa* plant was vegetatively propagated from an adult tree located in Ladang Sawit Kota Gelangi, Pahang (N3 57.130 E102 34.725). The species identity was confirmed by DNA barcoding, with four in-house reference samples (Voucher no. A2706, A2884, A4043, A4044).

The leaf samples were cryogenically ground with SPEX® SamplePrep 6875 Freezer/Mill (New Jersey, USA) for 1 min to produce uniform fine powder before being transferred into a pre-cooled Falcon tube, and freeze-dried for 36–48 hours in a Labconco® Freeze Dryer (Missouri, USA). Subsequently, the sample was extracted using methanol (0.1 g mL^{-1}) and sonicated for 15 min at room temperature using a Branson 5800 CPXH Ultrasonic Cleaner (Connecticut, USA) before filtered through Whatman™ 0.45 µm PTFE-B filter (Maidstone, UK) into a vial. Finally, the filtrate was diluted 3 × before subjected to HPLC analysis.

Preparation of calibration standard

Standard solutions of mitragynine were prepared in seven concentrations (1–500 µg mL^{-1}) by diluting a 1 mg mL^{-1} stock solution with methanol (Mudge & Brown 2017). These solutions were analysed using chromatographic techniques under specific conditions. Linearity was assessed by running triplicates of each concentration and determining the mean peak areas. Calibration curves were constructed using the mean peak areas obtained, allowing for the quantification of mitragynine in samples based on their corresponding peak areas in chromatograms.

Instrument and chromatographic conditions

The analysis was conducted using a Waters HPLC system (Massachusetts, USA), comprising a 600 controller, in-line degasser AF, 2707 autosampler, and 2996 photodiode array detector. Chromatographic separation was achieved using a Phenomenex Kinetex® 5 µm EVO C18 100 Å column (150 × 4.6 mm, 5 µm particle size) (California, USA), with a runtime of 25 minutes and an additional 5 minutes for methanol column equilibration at ambient temperature. The mobile phase consists of A: 5 mM ammonium bicarbonate buffer, pH 9.5, and B: 100% acetonitrile, following the protocol detailed in (Mudge & Brown 2017) with minor modifications. The chromatographic elution employed a binary gradient at a flow rate of 1 mL min^{-1} with a 10 µL sample injection, commencing at 20% A (0–2 min), transitioning to 30% A (2–5 min), 60% A (5–10 min), 80% A (10–15 min), remaining at 80% A (15–20 min), and concluding at 20% A (20–25 min). Detection was performed using a Waters 2996 photodiode array (PDA) detector at a wavelength of 226 nm, as described in (Mudge & Brown 2017). Data acquisition and processing were facilitated through the Empower Software System.

Method validation

The method was validated following the guidelines by The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) which include specificity, linearity, range, precision, accuracy, limits of detection (LOD) and quantification (LOQ) (ICH 2022).

The sample at its 100% working concentration was analysed using the protocol similar to that of the standards, allowing determination of peak area and retention time for MG. Linearity and range were established by generating a linear regression plot based on standard solution concentrations ranging from 1 to 500 µg mL^{-1}. Linearity was assessed through visual inspection of the linear relationship alongside statistical methods (ICH 2022), ensuring the appropriateness of the linearity. The range was defined to ensure that mitragynine in the sample fell within the specified concentration range.

The precision of an analytical method can be assessed by examining variations resulting from factors such as different days, analysts, and equipment (ICH 2022). Day-to-day variations were evaluated through intra-day and inter-day analyses. Intra-day analysis involved testing two samples in triplicate on the same day, while inter-day analysis replicated the same procedure on two consecutive days. The extent of dispersion was quantified by calculating the relative standard deviation (RSD) using the following formula:

$$\text{RSD} = \frac{\text{Standard deviation (SD)}}{\text{Mean}} \times 100\%$$

To evaluate accuracy, three distinct concentrations (low, medium, and high) of mitragynine standard were added to the sample at a working concentration of 0.03 g mL^{-1} as a spike (Takayama 2004). A matrix blank, devoid of the spike, served as a reference. The outcome was expressed as the percentage recovery of the assay, calculated using the provided formula.

$$\text{Recovery percentage} = \left(\frac{C_1 - C_2}{C_3}\right) \times 100\%$$

where C_1 = concentration of sample, C_2 = concentration of blank matrix, C_3 = concentration of added spike.

The LOD and LOQ were calculated based on signal-to-noise method. The recognition was conducted by evaluating signals from known low concentrations of reference standards with blank samples. The ratio used was 3:1 for LOD and 10:1 for LOQ to set up the minimum concentration of mitragynine that can be dependably quantified.

Mitragynine quantification

Each sample was analyzed in triplicates and the mitragynine concentration was determined based on the equation of the calibration curve (Fowble & Musah 2019).

RESULTS AND DISCUSSION

HPLC-PDA method development and optimisation

In a comparative pharmacokinetic study of traditional, formulated preparations and purified mitragynine after oral administration in rats (Avery et al. 2019), a HPLC-PDA method was developed for mitragynine quantification, targeting a much lower detection range. The calibration range was 100–10000 ng mL^{-1}, compared with 1–500 µg mL^{-1} in our study, whereby instead of 226nm, the detection and quantification of mitragynine was performed at λmax of 247nm, using Waters 996 PDA detector. Therefore, despite the existence of various methods for mitragynine quantification, development of HPLC methods is still necessary, taking into consideration the availability of different equipment models in different laboratories, constraints of resources, sample types and application purposes.

Method validation

Specificity

After assessing several columns for suitability, including Luna® C18 100 Å (250 × 4.6 mm, 5 µm particle size) and Kinetex® C18 (150 × 4.6 mm, 2.6 µm particle size), it was determined

that Kinetex® EVO C18 100 Å (150 × 4.6 mm, 5 µm particle size) (California, USA), provided the best peak resolutions and was thus chosen.

Result obtained during trial HPLC analysis using a solvent combination of 100% acetonitrile and 0.1% formic acid analysis was not satisfactory, with poor peak resolution (Figure 1A). In contrast, the mobile phase comprising 100% acetonitrile and 5 mM ammonium bicarbonate buffer (pH 9.5) (Mudge & Brown 2017) yielded good separation and resolution (Figure 1B). The major peak observed in the chromatogram profile in Figure 1B was anticipated to represent mitragynine, a predominant alkaloid compound in *M. speciosa* (Mudge & Brown 2017, Takayama 2004). Following optimisation of chromatographic resolution, mitragynine standard was used as a reference to precisely identify the retention time of mitragynine (Figure 1C).

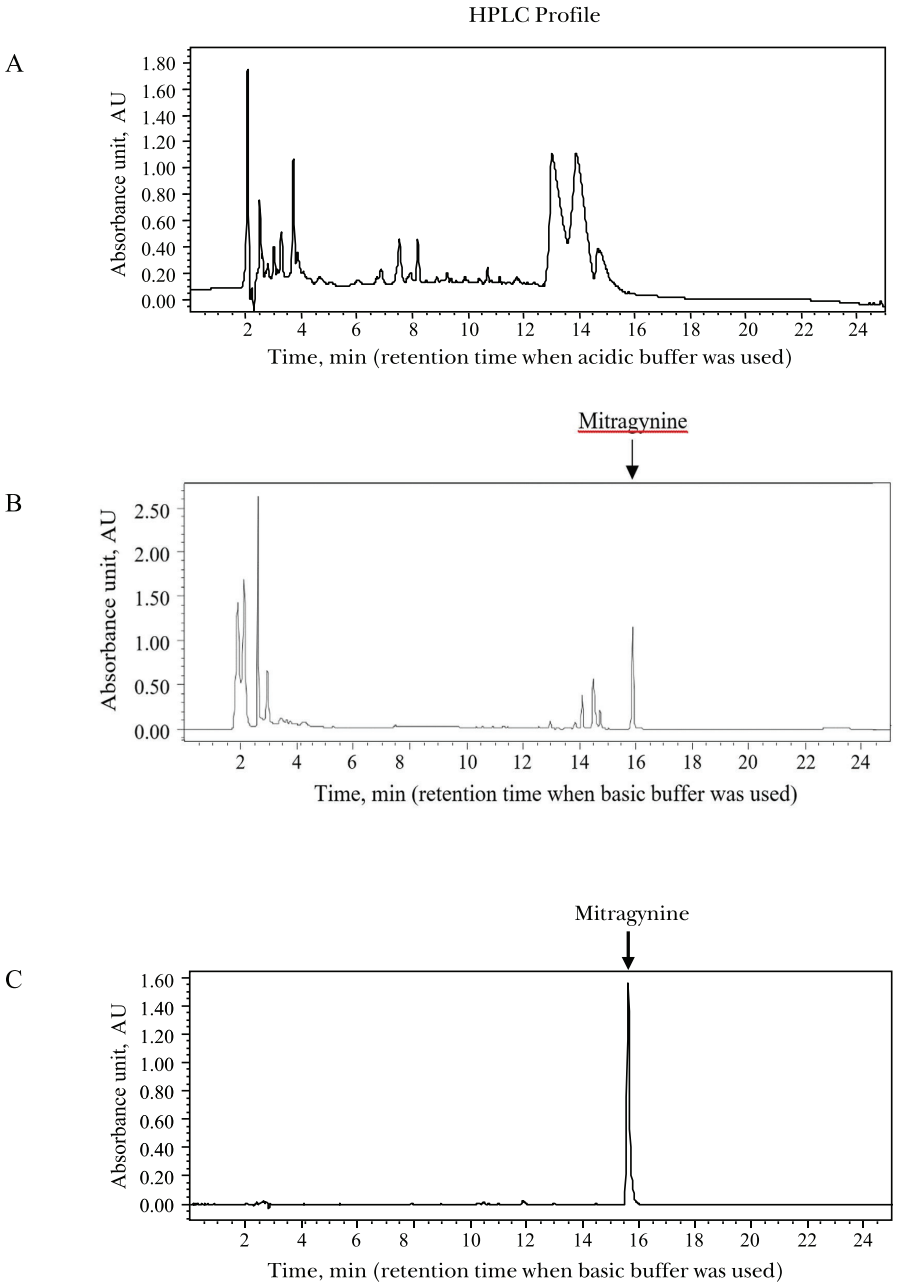

Figure 1 HPLC chromatograms of (A) Kratom leaf extract, using 100% acetonitrile and 5 mM ammonium bicarbonate buffer, (B) Kratom leaf extract, using solvent combination of 100% acetonitrile and 0.1% formic acid (C) Mitragynine reference standard using 100% acetonitrile and 5 mM ammonium bicarbonate buffer

Chromatogram profiles were examined at a maximum UV absorption detection wavelength of 226 nm, allowing for comparison of retention times and UV absorption spectra (Mudge & Brown 2017). Results indicated that the mean retention time for the mitragynine standard was 15.75 min. Notably, the chromatogram peak corresponding to mitragynine in the leaf extract sample closely aligned with the mean retention time of the reference standard at 15.75 min. The peak purity spectrum index data for both reference standard and the sample (Figure 2) indicated consistent UV spectra throughout the peak, signifying a pure mitragynine peak without interference from other co-eluting compounds.

It was reported that mitragynine has three stereoisomers, namely speciogynine, speciociliatine, and mitraciliatine (Karunakaran et al. 2022b), although up to 16 different stereoisomers are theoretically possible, considering the availability of three stereocenters and E-Z isomerism to the double bond of the methoxyacrylate group (Citti et al. 2023). From the sample spectrum index chromatography, four peaks were observed eluted before MG, all exhibiting UV spectra characteristics similar to MG (Figure 2). There is possibility that some of these peaks represent the stereoisomers of mitragynine. However, further analyses using reference materials are needed to confirm this postulation.

Linearity and range

Linearity was assessed through calibration curves generated from seven different concentrations of mitragynine standards. Adhering to the ICH guidelines (ICH 2022), which recommend a minimum of five concentrations for linearity

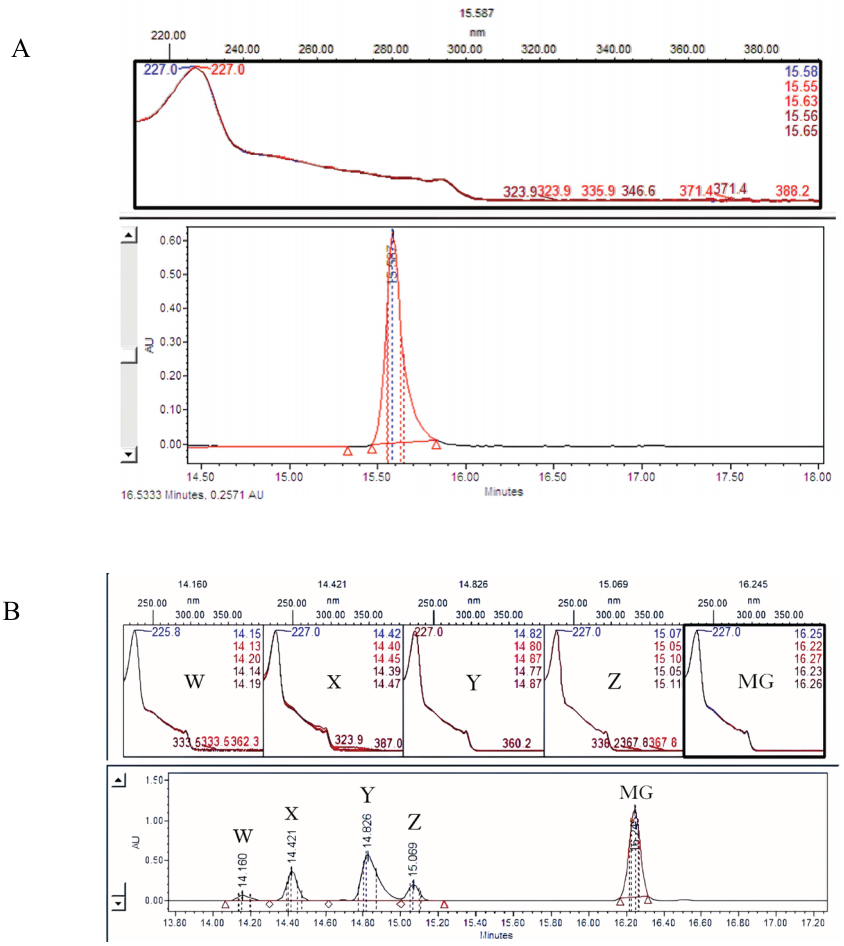

Figure 2 UV spectra for zoomed chromatogram of (A) Mitragynine reference standard, (B) Kratom leaf extract from freezed dried sample - MG refers to the mitragynine peak; four unknown peaks (W, X, Y, Z) eluted before MG, which share similar UV spectrum as MG

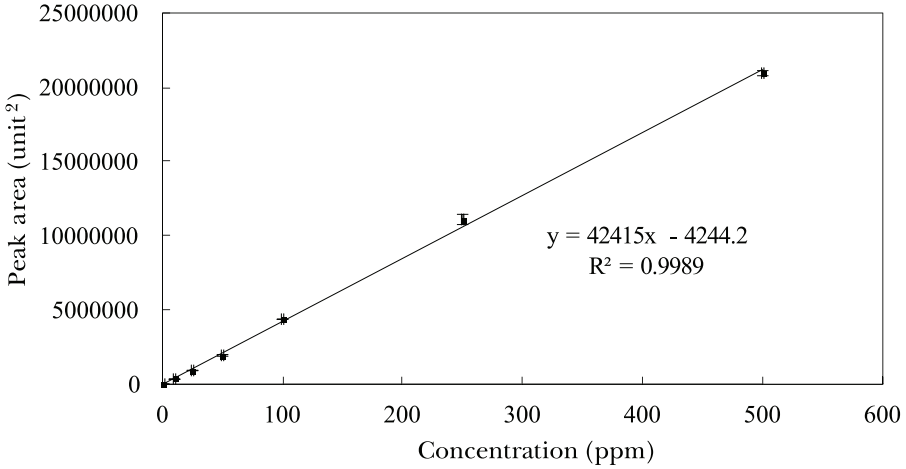

Figure 3 Calibration curve of mitragynine in the range of 1–500 µg mL^{-1}

determination, the inclusion of seven concentrations ensured the robustness of the linearity assessment. In Figure 3, the slope of the regression line for peak area exhibited a direct proportionality to the standard concentrations. Furthermore, determination coefficients (R^2) ≥ 0.99 were attained, indicating a linear relationship. The mitragynine concentration spanned from 1 to 500 µg mL^{-1}, a range carefully selected to ensure the method's adequacy in terms of linearity, accuracy, and precision when applied to samples containing mitragynine within the specified range (ICH 2022). Given mitragynine as a major alkaloid in the sample, its concentrations were expected to be substantial (Kruegel et al. 2019). Therefore, the selected range was deemed suitable, aligning with the anticipated mitragynine concentrations in the sample.

Precision and accuracy

Intra-day and inter-day analyses were performed on replicated extracts from the same leaf sample. The results demonstrated high intra-day and inter-day precision, with RSD values of 0.39% and 0.12%, respectively (Table 1). In general, RSD less than 2% is acceptable (Sim et al. 2022). Accuracy analysis was conducted by comparing extracted samples spiked at three levels, as indicated in Table 2, with a sample without MG standard spiking serving as the matrix blank. Our sample recovery rates fell within the range of 93% to 100%, indicative of high accuracy.

Limit of detection (LOD) and limit of quantification (LOQ)

The LOD and LOQ represent the minimum detectable and quantifiable concentrations of an analyte, respectively. Various methods can be employed for their calculation, including visual evaluation, signal-to-noise ratio, or standard deviation of the response and the slope (ICH 2022). In this study, the signal-to-noise method was selected. The determined values for LOD and LOQ within the concentration range of 1–500 µg mL^{-1} were 0.67 µg mL^{-1} and 1.51 µg mL^{-1}, respectively.

Mitragynine quantification

A linear calibration curve typically follows the equation y = mx + c, where m represents the slope of the regression line and c denotes the y-intercept. In the context of the calibration curve depicted in Figure 3, y signifies the peak area, while x represents the concentration of mitragynine. Mitragynine concentration (x) can be determined from the equation derived from the calibration curve, accounting for the corresponding dilution factor. Accordingly, the calculated mitragynine concentration for the sample using this method was 117.24 µg mL^{-1}, while the quantified mitragynine content was 5.86 mg g^{-1} (dried leaf). For comparison, an oven-dried sample was also analysed and yielded a concentration of 51.89 µg mL^{-1} and mitragynine content of 2.59 mg g^{-1} dried leaf.

Table 1 The average peak area for intra-day and inter-day analyses in triplicates (R1–R3), with corresponding standard deviation (SD) and relative standard deviation (RSD)

Sample	Replicate	Peak area (unit²)	Mean	Average	SD	RSD (%)
Intra-day I	R1	7435925				
	R2	7431841	7451459			
	R3	7486612		7443692	28919	0.39
Intra-day II	R1	7474091				
	R2	7489004	7410561			
	R3	7268588				
Inter-day I	R1	7435925				
	R2	7431841	7451459			
	R3	7486612		7457992	9239	0.12
Inter-day II	R1	7248975				
	R2	7567819	7248975			
	R3	7576780				

Table 2 Mitragynine standard spike recovery

Spike level	Concentration (μg mL^{-1})	Recovery (%)
Low	140	93.69
Medium	175	94.88
High	210	100.12

Freeze-dry versus oven-dry

Oven-drying is a common practice in preparing plant extracts for phytochemical analysis (Norhayati et al. 2018). Several HPLC methods previously reported for kratom involved drying of leaf samples, such as oven-dry at 45 °C (Parthasarathy et al. 2013) or air-dry (Karunakaran et al. 2022a). Based on studies on the effect of temperature on grape pomace, it was reported that oven drying methods can cause degradation, hydrolysis, and oxidation of the compounds of interest (Teles et al. 2017), particularly anthocyanins, but bioactive compounds with high antioxidant activity is less affected (Silva et al. 2020).

We compared the amount of mitragynine quantitated from this study with that of an oven-dried sample (fresh leaf from the same clone, dried in the oven at 45 °C overnight, ground with pestle and mortar, and homogenized using 500 μm sieve). It was found that the freeze-dried samples exhibited a higher mitragynine peak compared with the oven-dried samples (Figure 4). Correspondingly, the quantification of mitragynine revealed that the freeze-dry method yielded higher MG concentration (5.86 mg g^{-1} dried leaf), compared with the oven-dry (2.59 mg g^{-1} dried leaf) (Table 3). Notably, the difference between the mitragynine content is large, about two-fold. Thus it indicates possible negative effect of oven-drying on the mitragynine content of fresh leaf. The overnight heating at 45 °C could have led to mitragynine degradation. Not neglecting that the cryogenic grinding prior to freeze-drying also played an important role in preserving the mitragynine content in the fresh leaf. Therefore, we adopted freeze-drying in the current sample preparation method. Nevertheless, further investigations using leaf samples from different sources are needed to support this inference.

CONCLUSION

A highly precise and accurate HPLC-PDA method has been developed for mitragynine detection and quantification in fresh Kratom leaf. As Kratom is gaining attention as a potential medicinal plant with mitragynine being the

Table 3 The amount of mitragynine quantified in freeze-dried and oven-dried leaf samples per weight of dried-leaf

Sample	Replicate	Weight mg g^{-1} (dried leaf)	Mean
Oven-dried	R1	2.59	
	R2	2.59	2.59
	R3	2.60	
Freeze-dried	R1	5.90	
	R2	5.75	5.86
	R3	5.94	

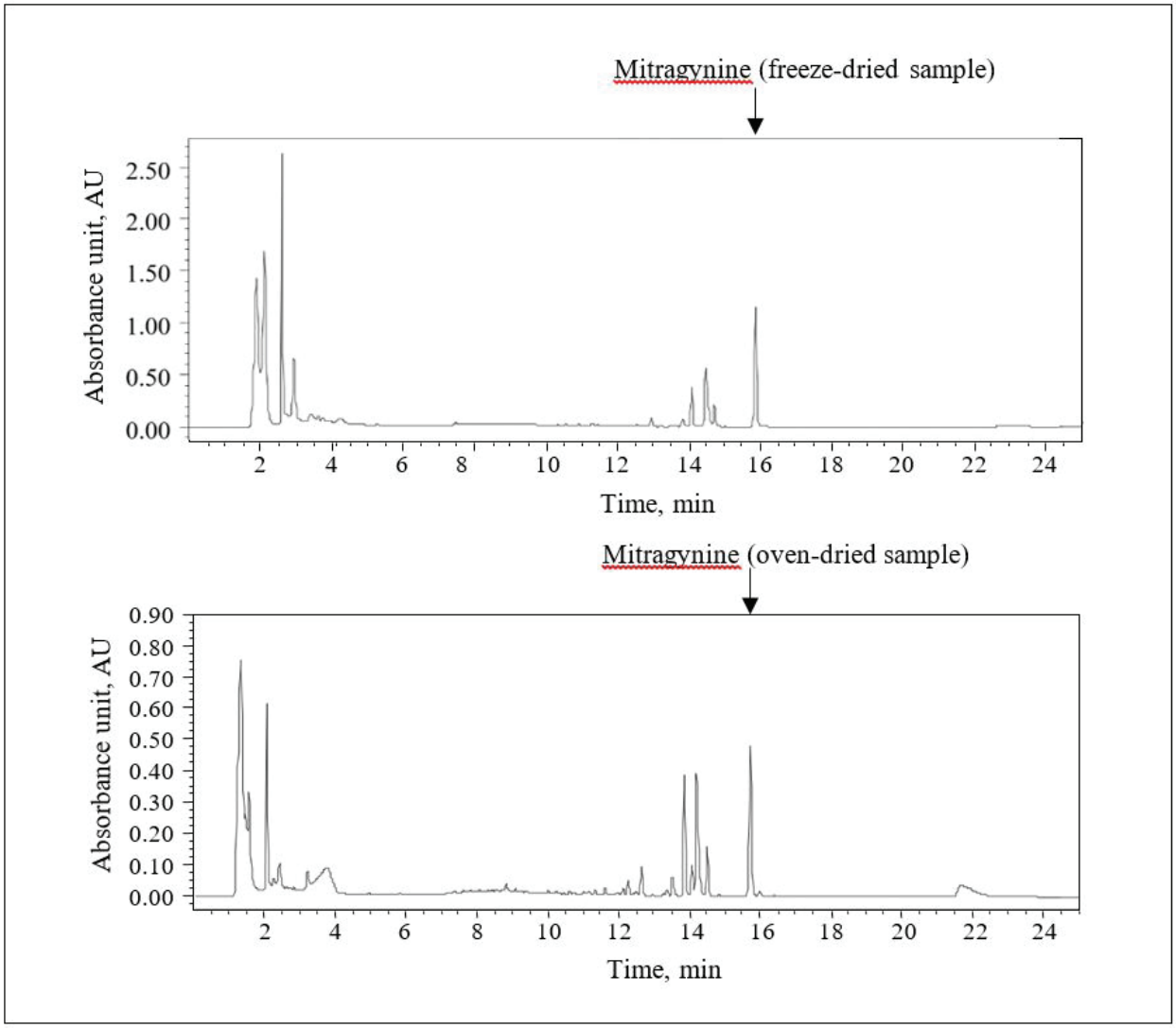

Figure 4 Comparison of HPLC chromatogram profiles between freeze-dried (top) and oven- dried (bottom) samples at the wavelength of 226 nm

main bioactive compound, this validated method will be useful for researchers who need to quantify mitragynine quantification in fresh leaf extracts and other dried samples possibly containing mitragynine, in complement to the existing HPLC methods, of which mostly cater for detection of mitragynine in minuscule amount.

In view of possible degradation of mitragynine caused by prolonged heating, we recommend freeze-drying method for sample preparation, when samples from fresh Kratom leaf or plant are used, for instance in pre- or post-harvest studies. It is even more crucial in gene expression studies involving mitragynine biosynthesis, whereby accurate mitragynine quantification is imperative.

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