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Research article

Association between kratom (*Mitragyna speciosa*) use and metabolic syndrome

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ABSTRACT

Background and aims: There are evidence about effects of kratom (*Mitragyna speciosa*) use on parameters related to metabolic syndrome (MetS). The present study aimed to determine the association between kratom use and MetS.
Methods: This study is a cross-sectional study of 581 subjects (kratom users and non-users) aged 18 and over from the Nam Phu sub-district, Surat Thani province, Thailand. The association was determined using multivariate logistic regression.
Results: MetS prevalence in kratom users and non-users was 11.9% (95% CI, 8.4–16.3%) and 21.6 % (95% CI, 17.1–26.8%), respectively. The use of kratom was associated with the lower odds of MetS (adjusted OR, 0.56; 95% CI, 0.33–0.96). Kratom use were associated with smaller waist circumference, lower triglycerides, and higher high-density lipoprotein.
Conclusions: The current study demonstrated a potential protective effect of kratom use against MetS.

1. Introduction

Kratom, or *Mitragyna speciosa* (Korth.) Havil., is a tropical herbaceous plant in the Rubiaceae family that is native to and widely distributed throughout Southeast Asia. It has been used medicinally and recreationally for over a century. It is used as medicine for treating a wide variety of symptoms and as a stimulant to boost energy and endurance, as well as tolerance for physically demanding work [1]. However, kratom remains illegal due to its classification as a narcotic crop in a number of countries, including Thailand, where possession and use of kratom are prohibited [2,3]. At the moment, kratom is used worldwide and is easily accessible through online purchasing [4].

Kratom contains over 40 alkaloids [4]. Numerous studies have focused on two alkaloids: mitragynine and 7-hydroxymitragynine [5, 6, 7]. A number of studies on the health benefits and consequences of kratom use are growing [8] as kratom consumption has increased in recent years in Europe and the United States [9] in addition to consumption in Southeast Asia, where kratom has been consumed over a century [10]. Nonetheless, the evidence for kratom's health benefits remains inconclusive, and kratom use patterns vary significantly across Asia, Europe, and North America [11].

Several previous studies, including one conducted in Thailand, discovered that kratom use has a mixed effect on lipid profiles, with dose and duration of use possibly playing a role [12, 13, 14]. Weight loss has been observed as an effect of kratom use in animal and human studies [15]. In kratom users, a brief increase in blood pressure and pulse rate was observed [16]. Additionally, kratom has been used traditionally to treat diabetes [4]. Hence, kratom use affected lipid profiles, body weight, blood pressure, and pulse rate. These metabolic conditions serve as diagnostic criteria for metabolic syndrome (MetS), a cluster of metabolic abnormalities characterized by a common pathophysiology including glucose intolerance, hypertension, dyslipidemia, and obesity [17]. With the effects of kratom on each metabolic parameter, the current study aimed to determine the effect of traditional kratom use on MetS.

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2. Subjects

The study site was Nam Phu sub-district, Ban Na San district, Surat Thani province in the south of Thailand. The study subjects were randomly selected from two sub-populations—users and non-users of kratom. The inclusion criteria were that subjects must be at least 18 years old and have lived in the Nam Phu subdistrict for at least one year. To be regarded as a kratom user, he or she must used kratom within the past 12 months and have registered with the sub-district in accordance with the Nam Phu Charter, a guideline for personal kratom use commissioned by the Nam Phu sub-district. Non-user refers to individuals who have not used kratom in the past 12 months. Pregnant women and those with a history of illicit drug abuse were excluded. To account for the effect of age, subjects from the user and non-user groups were matched by age. Non-users were chosen from the same age group as kratom users. Age groups for the matching were as follows: 18–20, 21–25, 26–30, 31–35, 36–40, 41–45, 46–50, 51–55, 56–60, 61–65, 66–70, 71–75, 76–80, 81–85, and 86 years and older. The study objectives and protocol were explained to all invited individuals. Those who agreed to participate had to provide written consent before participating in this study. Subjects were interviewed on the same day. After the interview, the appointment for physical examination and blood sample collection on another day were made.

3. Materials and methods

3.1. Study design and study setting

This research design is a cross-sectional study of kratom users and non-users. The study site was Nam Phu sub-district, Ban Na San district, Surat Thani province in the southern region of Thailand. The sub-district has a flat topography with the sub-forest area serving as a natural habitat for kratom plants. Plantings of kratom trees can be seen along house fences. The Nam Phu sub-district is among the jurisdictions where possession and traditional use of kratom is permitted under the supervision of the Office of Narcotics Control Board, Ministry of Justice. The community established the Nam Phu Charter, a guideline for personal kratom use in 2017 through a participatory process [14].

3.2. Measurement

3.2.1. Biochemical analysis

Subjects were advised to abstain from food and drink after 8:00 p.m. on the day before sample collection. On the sample collection day, at 8 a.m., an appointment was made at Ban Yang Ung Public Health Promotion Hospital. Blood pressure was measured. A medical technologist took a blood sample from each study subject. Each blood sample was sent for biochemical analysis (fasting glucose, serum lipid, and mitragynine) within one hour of collection. The laboratory was accredited by the Thailand's Medical Technology Council.

3.2.2. Metabolic syndrome diagnosis

In this study, subjects were diagnosed with MetS following the diagnostic criteria by "A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity [17]. To be diagnosed with MetS, at least three of the following five criteria must be met: 1) waist circumference (WC) $>$ 90 cm for men and $>$80 cm for women, 2) triglycerides (TG) 150 mg/dL or on medication for elevated TG, 3) high-density lipoprotein (HDL) 40 mg/dL for men and 50 mg/dL for women, or on medication for reduced HDL, 4) systolic blood pressure (BP) 130 and/or diastolic BP $\geq$ 85 mmHg, or on antihypertensive medication, and 5) fasting glucose (FG) $\geq$ 100 mg/dL or on medication for elevated blood glucose.

3.3. Statistical analysis

The descriptive statistics were used to summarize the subjects' characteristics (frequency, percentage, arithmetic mean, and standard deviation). In bivariate analysis, the chi-square test, analysis of variance, and Mann-Whitney U test were used. The bivariate analysis was used to initially explored possible associations. Independent effects of kratom use and other factors on MetS were determined using multivariate logistic regression. The regression model was used to adjust for confounding effects and estimate odds ratio (OR) with 95% confidence interval (CI). All analyses were conducted using R 3.5.2 on RStudio® 1.2.1335. The level of significance used was at p-value $<$0.05.

4. Results

As shown in Table 1, the study included 285 users of kratom and 296 non-users. The unequal numbers between the two groups were caused by 11 kratom users who did not show up on the day of blood sample collection and were thus excluded from the analysis. Serum mitragynine was tested in the kratom user group with the median of 90.86 ng/mL (interquartile range, 14.7–380.7 ng/mL). Men dominated the kratom user group (78.6%), but comprised a minority of the non-user group (29.7%). An average age was around 55 years old in both groups. Kratom users had significantly lower WC and BMI. Diastolic BP was higher in kratom users than in non-users, while systolic BP did not differ. Kratom users had a significantly higher HDL level than non-users. The proportions of medications used for diabetes, hypertension, and dyslipidemia were comparable. Kratom users drank and smoked more than non-users, and exercised less.

Table 2 shows the prevalence of MetS by kratom use status and demographic characteristics of study subjects along with p-values from the bivariate analysis. Kratom use, male sex, smoking, and drinking alcohol seemed to be related with a decreased risk of MetS.

Table 3 shows the relationship between kratom use and each MetS diagnostic criterion. Kratom use was related with a 60% and 40% decrease in chance of elevated WC and elevated TG, respectively. The prevalence of reduced HDL was substantially lower among kratom users. The prevalence of elevated FG and elevated BP did not differ among kratom users and non-users.

The results of multivariate logistic regression are depicted in Figure 1. After adjustment for sex, age group, smoking status, alcohol drinking, and exercise, the adjusted OR for kratom use was 0.56 (95% CI, 0.33–0.96; p-value, 0.035). Alcohol drinking was linked to a decreased risk of MetS. Physical inactivity was linked to a greater likelihood of MetS.

The association between kratom leaves consumed per day and MetS was explored. The prevalence of MetS by quartile of kratom leaves consumed per day were as follows: 5.0% (Q1), 16.2% (Q2), 7.2% (Q3), and 9.6% (Q4). The association was not statistically significant (p-value, 0.363).

The prevalence of MetS by alcohol drinking status and kratom use is summarized in Table 4. MetS was less prevalent in kratom users than in non-users, regardless of alcohol consumption. The Mantel-Haenzel OR for kratom use and MetS was 0.57, which was similar to the OR estimated by logistic regression (Figure 1).

5. Discussion

This study demonstrated an association between kratom use and a decreased likelihood of MetS. This was attributable to the effects of kratom use on WC, TG, and HDL—which are three of the five diagnostic criteria of MetS.

Table 1. Characteristics of study subjects.

Characteristics	Statistics	User (n = 285)	Non-user (n = 296)	P-value
Sex (male)	n (%)	224 (78.6)	88 (29.7)	<0.001[a]
Age (years)	Mean ± SD	55.77 ± 11.44	55.73 ± 11.97	0.963[b]
Waist circumference (cm)	Mean ± SD	83.41 ± 9.77	86.11 ± 10.17	0.001[b]
BMI (kg/m^2)	Mean ± SD	23.09 ± 3.92	25.24 ± 4.76	<0.001
Overweight (25.0–29.9)	n (%)	64 (22.5)	98 (33.1)	<0.001[a]
Obesity (30 or more)	n (%)	14 (4.9)	43 (14.5)	
Systolic BP (mmHg)	Mean ± SD	116.95 ± 15.17	116.42 ± 14.49	0.670[b]
Diastolic BP (mmHg)	Mean ± SD	72.38 ± 11.07	70.49 ± 11.97	0.049[b]
Fasting glucose (mg/dL)	Mean ± SD	95.49 ± 32.44	96.60 ± 23.81	0.640[b]
HDL (mg/dL)	Mean ± SD	56.68 ± 16.31	53.56 ± 13.61	0.013[b]
Triglycerides (mg/dL)	Mean ± SD	114.57 ± 80.13	125.48 ± 68.11	0.077[b]
Use of anti-diabetic drug	n (%)	28 (9.8)	26 (8.8)	0.671[a]
Use of anti-hypertensive drug	n (%)	78 (27.4)	79 (26.7)	0.854[a]
Use of anti-lipidemic drug	n (%)	58 (20.4)	68 (23.0)	0.443[a]
Current smoker	n (%)	154 (54.0)	39 (13.2)	<0.001[a]
Current drinker	n (%)	74 (26.0)	23 (7.8)	<0.001[a]
Exercise: active (30 min/time, and 3 times/week or more)	n (%)	80 (28.1)	114 (38.5)	0.008[a]

[a] Chi-square test.
[b] t-test.

5.1. MetS prevalence in kratom users

The prevalence of MetS in kratom users in this study was 11.9% (95% CI, 8.4–16 .3%). The prevalence of MetS in Thai population was 24% [18], while the global estimate of MetS prevalence was around 25% [19], and the prevalence in the adult US population was 22.9% [20]. In essence, the prevalence of MetS in kratom users was substantially lower than in the general population, whereas the prevalence of MetS in this study's control group is equivalent to the general population. The current study found that women have twice the prevalence of MetS as men. This is consistent with the findings of previous research [21].

The observed association between kratom use and a decreased risk of MetS was due to kratom's effects on WC, TG, and HDL. The prevalence of elevated WC, TG, and HDL in the non-user group was comparable to that previously reported in the literature. According to a study in Asian adults, the prevalence of elevated WC was 58.1% [22], while it was 61.8% in our control group. In kratom users, the prevalence was 35.4%. Reduced HDL prevalence was 33% in European men and 40% in European women [23], compared to 33.1% in our control group. In kratom users, the prevalence was 17.5%. The prevalence of elevated TG was 31.6% in US adults [24], while the prevalence was 29.1% in our control group. Prevalence was found to be 20.0 percent among kratom users. Previous study from Malaysia found the result like our study by Kratom user have a HDL higher than non-user at $p < 0.05$ and no significant between 2 group of blood glucose [13]. Our results showed no difference in blood pressure between the two groups, whereas Abdullah and Singh (2021) found that

Table 2. Prevalence of MetS among study subjects by characteristics.

Characteristics	Total (N = 581)				User (n = 285)		Non-user (n = 296)	
	n	%	95% CI	p-value	%	95% CI	%	95% CI
Total	581	16.9	13.9–20.2		11.9	8.4–16.3	21.6	17.1–26.8
Sex				0.005*				
Male	312	12.8	9.3–17.0		11.2	7.4–16.0	17.0	9.9–26.6
Female	269	21.6	16.8–27.0		14.8	7.0–26.2	23.6	18.0–29.9
Age group				0.258				
<40	46	17.4	7.8–31.4		19.0	5.4–41.9	16.0	4.5–36.1
40–49	129	10.9	6.1–17.5		11.9	4.9–22.9	10.0	4.1–19.5
50–59	175	19.4	13.8–26.1		12.5	6.4–21.3	26.4	17.6–37.0
60–69	157	19.7	13.8–26.8		9.8	4.3–18.3	30.7	20.5–42.4
70 and more	74	14.9	7.7–25.0		11.4	3.2–26.7	17.9	7.5–33.5
Smoking				0.025*				
Current smoker	193	11.9	7.7–17.3		12.3	7.6–18.6	10.3	2.9–24.2
No	388	19.3	15.5–23.6		11.5	6.6–18.2	23.3	18.3–29.0
Alcohol				0.002*				
Current drinker	97	6.2	2.3–13.0		4.1	0.8–11.4	13.0	2.8–33.6
No	484	19.0	15.6–22.8		14.7	10.2–20.2	22.3	17.5–27.8
Exercise				0.070				
Active	194	12.9	8.5–18.4		10.0	4.4–18.7	14.9	8.9–22.8
Inactive	387	18.9	15.1–23.1		12.7	8.5–18.0	25.8	19.6–32.8

* P-value <0.05.

Table 3. Association between kratom use and each MetS diagnostic criterion.

MetS parameter	Kratom use	Prevalence		OR	95% CI	P-value[a]
		%	95% CI			
Elevated WC	Kratom user	35.4	29.9–41.3	0.4	0.2–0.5	<0.001*
	Non-user	61.8	56.0–67.4	Ref.		
Elevated FG	Kratom user	23.9	19.0–29.2	0.7	0.5–1.1	0.111
	Non-user	29.7	24.6–35.3	Ref.		
Elevated BP	Kratom user	16.5	12.4–21.3	1.0	0.7–1.6	0.929
	Non-user	16.2	12.2–20.9	Ref.		
Elevated TG	Kratom user	20.0	15.5–25.1	0.6	0.4–0.9	0.012*
	Non-user	29.1	23.9–34.6	Ref.		
Reduced HDL	Kratom user	17.5	13.3–22.5	0.4	0.3–0.6	<0.001*
	Non-user	33.1	27.8–38.8	Ref.		

[a] Logistic regression.
* P-value <0.05.

tachycardia and hypertension are common adverse cardiovascular effects of kratom consumption [25].

5.2. Association between kratom use and MetS

The primary finding of this study was an association between kratom use and a decreased risk of MetS. This study, to our knowledge, is among the first reports regarding the association. Nonetheless, studies on certain herbal regimens have demonstrated their ability to prevent MetS. A systematic review of randomized controlled trials found that various herbal regimens significantly reduced FG, TG, SBP, and DBP [26].

Mitragynine inhibits cycloxygenase-2 (COX-2) expression [27], which is positively associated with serum triglycerides [28]. In addition, Shamima et al. (2012) showed that mitragynine activates opioid receptors [29]. Opioid receptors have a role in lipid and energy metabolism control [30] and positive influence on glucose metabolism regulation [31]. Therefore, the effect of kratom on metabolic syndrome is possibly due to effects of mitragynine on COX-2 expression and opioid receptors.

Table 4. Association between kratom use and MetS by alcohol drinking status.

Current drinker	Kratom use	n	MetS	
			%	95% CI
Yes	User	74	4.1	0.8–11.4
	Non-user	23	13.0	2.8–33.6
No	User	211	14.7	10.2–20.2
	Non-user	273	22.3	17.5–27.8
Mantel-Haenzel common OR (95% CI)			0.57 (0.36–0.90)	
P-value			0.017	

In Thailand, kratom is primarily consumed through the chewing of fresh leaves [32]. Under the Nam Phu Charter, members of the Nam Phu subdistrict are permitted to consume kratom by chewing its leaves, which is considered the traditional method of kratom consumption. The oral route allows for rapid absorption of the majority of kratom's active constituents [33]. The protective effect of kratom against MetS may be due to phenolic compounds in kratom leaves. In a previous study, consuming food high in phenolic compounds was shown to prevent MetS [34]. Phenolic compounds and flavonoids, which have antioxidant and antimicrobial properties, are among the active ingredients found in kratom [35].

5.3. Limitations

The major limitation of this study is its cross-sectional design. As a result, the association between kratom use and a decreased risk of developing MetS observed in this study cannot be interpreted as causal. There was a sex imbalance between kratom users and non-users. Females made up the majority of non-users, whereas males made up the majority of users. Thai females are more likely to be obese [36]. Hence, sex confounded the association between kratom use and MetS. The multivariate regression analysis was used to account for this confounding effect of sex (Figure 1). There was no adjustment for some potential confounding variables, such as dietary behavior. Further research incorporating these factors and using a prospective design is warranted.

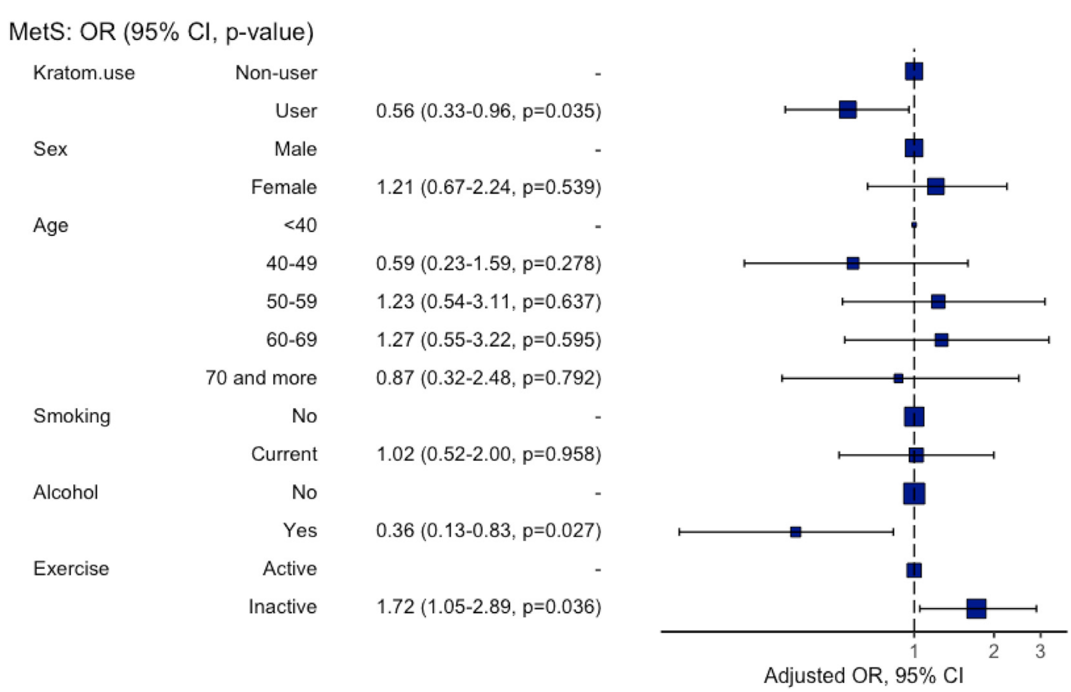

Figure 1. Factors associated with MetS (multivariate logistic regression).

5.4. Conclusion

This study discovered the association between kratom use and a lower risk of MetS. This was due to kratom's effects on WC, TG, and HDL—three of the five diagnostic criteria of MetS.

Declarations

Author contribution statement

Aroon La-up; Paleeratana Wongrit; Wiraphon Chaichan & Udomsak Saengow: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Apinun Aramrattana: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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