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Hematological and clinical-chemistry parameters of kratom users: a comparative study of users and non-users in Southern Thailand

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Kratom (*Mitragyna speciosa*) has transitioned from a traditional Southeast Asian remedy to a substance of global interest. The existing evidence on its safety is contradictory, with case reports from Western countries suggesting organ toxicity, while community-based studies in traditional settings show minimal adverse effects. This study aimed to evaluate the physiological impact of long-term, traditional kratom use in an endemic region of Southern Thailand. A cross-sectional study was conducted among 285 traditional kratom users and 296 non-user controls from the same community. Key hematological and clinical-chemistry parameters, including liver and kidney function markers, were compared. Analyses were stratified by sex and kratom use characteristics (duration and quantity) to assess subgroup-specific effects. Analysis of Covariance (ANCOVA) was used to adjust for potential confounding variables, including age, sex, BMI, smoking, and alcohol consumption. After adjusting for confounders, no clinically significant differences were observed in hepatic or hematological parameters, with mean values for both groups remaining within normal clinical reference ranges. However, kratom use was significantly associated with lower serum creatinine ($p < 0.001$) and higher eGFR ($p = 0.002$), a finding likely attributable to the lower BMI in the user group. Stratified analyses by duration and quantity revealed no clear dose–response relationship regarding organ toxicity, although higher consumption was associated with altered renal markers. These findings suggest that within a traditional-use setting, chronic kratom consumption was not associated with clinically significant hepatic or hematological toxicity. The observed association with renal markers is explained by differences in body composition rather than a direct pharmacological effect. These findings underscore the critical importance of controlling for lifestyle and demographic confounders in evaluating the health impacts of kratom.

Keywords Kratom, Health, Parameters, Toxicity, Health impact

Kratom (*Mitragyna speciosa* Korth.), a tropical evergreen tree native to Southeast Asia, has been used for centuries in traditional medicine, particularly in Thailand, Malaysia, and Indonesia[1,2]. The leaves of the plant are traditionally consumed by chewing or brewing them as a tea to alleviate fatigue, enhance work productivity, and manage pain[1]. The plant's pharmacological effects are primarily attributed to its active alkaloids, mitragynine and 7-hydroxymitragynine, which exert complex, dose-dependent effects, ranging from stimulant-like activity at low doses to opioid-like analgesia at higher doses[2,3].

In recent years, kratom has gained significant popularity beyond its traditional contexts, with a growing global user base seeking it for therapeutic and recreational purposes[4]. This expansion, coupled with a shifting legal landscape, including its decriminalization in Thailand in 2021, has intensified the scientific and regulatory debate surrounding its safety profile. The existing evidence remains fragmented and often contradictory. On the one hand, numerous case reports have suggested a potential link between kratom consumption and organ toxicity, particularly hepatotoxicity and nephrotoxicity[5]. On the other hand, some systematic reviews and community-

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based studies, especially among traditional users in Malaysia, have reported no significant alterations in major hematological or biochemical parameters, even with long-term, high-quantity use[6].

This conflicting evidence highlights a critical knowledge gap, particularly regarding the long-term physiological effects of traditional consumption patterns in endemic regions. This ambiguity leaves kratom users, health providers, and policymakers without evidence-based guidance and robust data to inform harm-reduction strategies. Southern Thailand, where kratom use is a long-standing cultural practice, presents a unique opportunity to address this gap[7]. The region provides a valuable setting to compare habitual users and non-users who share a similar demographic and environmental context. A systematic investigation is urgently needed to provide robust, population-based evidence on kratom's subclinical health impacts, which is essential for informing public health policy, harm-reduction strategies, and clinical guidance for healthcare providers. Furthermore, the relationship between the dose and duration of use and potential physiological changes remains poorly understood[4,5].

It should be noted that the participants in this study were recruited as part of a larger community-based health surveillance project in the Nam Phu sub-district. Previous reports from this cohort have focused specifically on lipid profiles[8] and metabolic syndrome parameters[9]. However, the present study investigates entirely distinct physiological parameters that have not been reported elsewhere. Unlike the previous publications, which were restricted to metabolic indices, this study provides a comprehensive analysis of hematological parameters (complete blood count) and clinical chemistry markers specifically related to liver and kidney function. This distinct dataset addresses the need for a broader understanding of the physiological safety profile of traditional kratom users beyond metabolic health.

Therefore, this study aimed to (1) compare key hematological and clinical-chemistry parameters, including liver and kidney function markers, between traditional kratom users and non-users in a large community-based sample in Southern Thailand, and (2) examine the association between the duration and quantity of kratom consumption and these physiological parameters among users.

Materials and methods

Study design and setting

This study utilized data from a large cross-sectional project conducted in the Nam Phu sub-district, Surat Thani province, located in Southern Thailand. The characteristics of the study population and data collection procedures have been described in detail elsewhere[8,9]. The present study focuses on a novel, in-depth analysis of hematological and a broad range of clinical-chemistry parameters. This area was selected as the community has been permitted to use kratom according to traditional practices under the "Nam Phu Sub-district Charter," a local community agreement established in 2017. The reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[10].

Study participants

The study population consisted of 581 individuals aged 18 years or older who had resided in the Nam Phu sub-district for at least one year. Participants were categorized into two groups: Kratom users, defined as individuals who had used kratom within the past 12 months and were officially registered under the community charter agreement; and non-users, defined as individuals with no history of kratom use within the past 12 months. To control for the potential confounding effect of age, the non-user group was matched to the user group to ensure a similar age structure. Exclusion criteria for all participants included pregnancy, a history of illicit substance use (other than kratom), and the inability to communicate clearly. All participants were fully informed about the study's objectives and procedures, and written informed consent was obtained prior to their enrollment.

Data collection and measurements

Data were collected through face-to-face interviews using a structured questionnaire administered by trained research staff. The questionnaire gathered information on sociodemographic characteristics, health-related behaviors, medical history, and current medication use. For kratom users, data on the duration of use (in years) and the daily quantity of consumption (in number of leaves) were also collected. Height and weight were measured to calculate the body mass index (BMI).

The questionnaire was developed based on a literature review and validated for content validity by five experts using the Index of Item-Objective Congruence (IOC). Only items with an IOC index ≥ 0.5 were included in the final version. The English version of the questionnaire is provided as "Supplementary File S1".

Laboratory procedures

Participants were instructed to fast for 12 h overnight before blood sample collection. On the morning of the appointment, a 3-ml sample of venous blood was drawn by a certified medical technologist at the Ban Yang Ung Health Promoting Hospital. The samples were then transported to the laboratory unit of Ban Na San Hospital, which is accredited by the Medical Technology Council of Thailand, for analysis within one hour of collection. For hematological analysis, a complete blood count (CBC) was performed using an automated hematology analyzer (Nihon Kohden Cell Counter, models 7222 and 8222). Concurrently, clinical-chemistry parameters, including liver function tests, kidney function tests, and blood glucose/HbA1c levels were analyzed using an automated chemistry analyzer (Dimension EXL 200).

Statistical analysis

All data were analyzed using SPSS version 30.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including means, standard deviations (SD), frequencies, and percentages, were used to summarize the baseline characteristics of the study participants. Bivariate analyses were conducted to compare the two groups. The

Independent Samples t-test was used for continuous variables (e.g., hematological and biochemical parameters), while the Chi-square test was used for categorical variables (e.g., sex, smoking status). Furthermore, analysis of covariance (ANCOVA) was used to compare the mean hematological and clinical-chemistry parameters between kratom users and non-users, as well as among kratom users stratified by duration and quantity of use, after controlling for potential confounding variables. Covariates included in the adjusted model were age, sex, body mass index (BMI), current smoking status, and current alcohol consumption. A p-value of < 0.05 was considered statistically significant for all tests.

Results

Sociodemographic characteristics and health behaviors

A total of 581 participants were included in the final analysis, comprising 285 kratom users and 296 non-users. The sociodemographic characteristics and health behaviors of the participants are presented in Table 1. The mean age of the two groups was nearly identical (55.8 ± 11.4 vs. 55.7 ± 12.0 years, $p = 0.963$). However, significant baseline differences were observed for several key variables. The kratom user group had a significantly higher proportion of males (78.6% vs. 29.7%, $p < 0.001$) and a lower mean BMI (23.1 ± 3.9 vs. 25.2 ± 4.8 kg/m^2, $p < 0.001$).

Regarding health behaviors, kratom users reported significantly higher rates of current smoking (54.0% vs. 13.2%, $p < 0.001$) and current alcohol consumption (26.0% vs. 7.8%, $p < 0.001$). Conversely, non-users were more likely to engage in regular exercise (38.5% vs. 28.1%, $p = 0.008$). A history of cannabis and methamphetamine use was also more prevalent in the kratom user group. No significant differences were found in the use of prescribed medications for hypertension or diabetes between the groups.

Comparison of hematological parameters

The comparison of hematological parameters is shown in Table 2. In the unadjusted analysis, kratom users exhibited significantly higher mean values for white blood cells (WBC), red blood cells (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), and significantly lower platelet counts (all $p < 0.05$).

However, after adjusting for age, sex, BMI, current smoking, and current alcohol consumption, all of these differences became non-significant ($p > 0.05$). Importantly, the mean values for all hematological parameters in both groups fell within the normal reference ranges.

Comparison of clinical-chemistry parameters

The comparison of key clinical-chemistry markers for liver and kidney function is detailed in Table 3. Liver Function: In the unadjusted analysis, users showed slightly higher alkaline phosphatase levels ($p = 0.022$) and lower albumin levels ($p = 0.008$). However, after adjustment for confounders, no statistically significant differences were observed for any liver function markers, including AST, ALT, alkaline phosphatase, bilirubin, or plasma proteins (all $p > 0.05$). Kidney Function: A significant association was found with markers of renal function. In the adjusted model, kratom users had significantly lower serum creatinine levels (adjusted mean, male: 0.89 vs. 0.99 mg/dL, $p < 0.001$) and consequently a significantly higher estimated glomerular filtration rate (eGFR) (adjusted mean: 95.42 vs. 91.55 mL/min/1.73m^2, $p = 0.002$) compared to non-users. Glycemic Control: There were no significant differences in fasting blood glucose or HbA1c between the two groups in either the unadjusted or adjusted analyses.

Stratified analysis by duration and quantity of use

To control for potential confounders, an ANCOVA was conducted, adjusting for age, BMI, sex, smoking, and drinking history (Table 4). After adjusted comparison, long-term users (≥ 5 years) exhibited significantly lower levels of glucose ($p < 0.001$), HbA1c ($p = 0.017$), total protein ($p = 0.023$), albumin ($p < 0.001$), total bilirubin ($p = 0.035$), and direct bilirubin ($p = 0.016$) compared to short-term users (< 5 years). Quantity of Use (Table 5): After adjustment for potential confounders (age, BMI, sex, smoking, and alcohol drinking), significant differences were observed in renal function markers and serum protein levels. Users consuming higher quantities of kratom

Characteristics	Kratom users (n = 285)	Non-users (n = 296)	p-value
Age (year), Mean ± SD	55.8 ± 11.4	55.7 ± 12.0	0.963
Sex (male), n (%)	224 (78.6)	88 (29.7)	< 0.001
BMI (kg/m^2), Mean ± SD	23.1 ± 3.9	25.2 ± 4.8	< 0.001
Current smoking, n (%)	154 (54.0)	39 (13.2)	< 0.001
Current drinking, n (%)	74 (26.0)	23 (7.8)	< 0.001
Exercise (≥ 3 times/week), n (%)	80 (28.1)	114 (38.5)	0.008
History of cannabis use, n (%)	44 (15.4)	11 (3.7)	< 0.001
History of methamphetamine, n (%)	11 (3.9)	3 (1.0)	0.030
Use of antihypertensive medication, n (%)	78 (27.4)	79 (26.7)	0.854
Use of antidiabetic medication, n (%)	28 (9.8)	26 (8.8)	0.666
Regular use of other herbal supplements, n (%)	50 (17.5)	44 (14.9)	0.381

Table 1. Sociodemographic characteristics and health behaviors of participants, stratified by kratom use.

Parameters	Unadjusted mean (SD)			Adjusted mean (95% CI)			Reference range
	Users (n = 285)	Non-users (n = 296	*p*-value	Users, n = 285)	Non-users, n = 296	*p*-value	
WBC (10^3/μL)	8.03 ± 2.01	7.43 ± 2.20	< 0.001	7.72 (7.47–7.97)	7.73 (7.49–8.00)	0.943	4.0–9.0
RBC (10^6/ μL)	4.95 ± 0.54	4.77 ± 0.55	< 0.001	4.88 (4.81–4.94)	4.84 (4.78–4.90)	0.401	3.8–5.3
Hemoglobin (g/dL) (Male)	14.58 ± 1.38	14.61 ± 1.55	0.870	14.58 (14.40–14.77)	14.61 (14.31–14.91)	0.875	14–18
Hemoglobin (g/dL) (Female)	12.90 ± 1.33	12.63 ± 1.42	0.188	12.83 (12.44–13.21)	12.72 (12.52–12.92)	0.649	12–16
Hematocrit (%) (Male)	44.96 ± 3.81	45.04 ± 4.44	0.871	44.89 (44.47–45.50)	44.96 (44.13–45.80)	0.963	42–52
Hematocrit (%) (Female)	40.40 ± 3.84	39.80 ± 3.80	0.275	40.26 (39.25–41.26)	40.02 (39.49–40.54)	0.695	36–48
MCV (fL)	89.27 ± 7.65	87.24 ± 8.70	0.003	88.07 (87.08–89.07)	88.40 (87.42–89.37)	0.672	80–100
MCH (pg)	28.87 ± 2.97	27.88 ± 3.30	< 0.001	28.33 (27.95–28.71)	28.41 (28.04–28.78)	0.776	28–32
MCHC (g/dL)	32.29 ± 0.83	31.90 ± 0.95	< 0.001	32.10 (32.00–32.21)	32.08 (31.98–32.19)	0.787	31–35
RDW (%)	13.38 ± 1.47	13.47 ± 1.44	0.463	13.34 (13.16–13.52)	13.50 (13.32–13.68)	0.241	10.0–16.5
Platelets (10^3/μL)	264.10 ± 58.30	276.40 ± 63.26	0.015	271.45 (263.89–279.02)	269.31 (261.91–276.71)	0.712	150–350
Neutrophils (%)	52.36 ± 10.23	51.89 ± 10.16	0.574	51.66 (50.37–52.95)	52.56 (51.03–53.83)	0.359	42–85
Lymphocytes (%)	37.05 ± 9.77	38.03 ± 9.49	0.220	38.12 (36.91–39.32)	37.01 (35.83–38.19)	0.232	11–49
Monocytes (%)	5.92 ± 1.65	5.79 ± 1.61	0.340	5.80 (5.59–6.00)	5.92 (5.72–6.12)	0.442	0–9
Eosinophils (%)	4.60 ± 3.11	4.24 ± 3.42	0.177	4.39 (3.97–4.80)	4.45 (4.04–4.85)	0.851	0–6
Basophils (%)	0.06 ± 0.24	0.05 ± 0.22	0.636	0.05 (0.02–0.08)	0.06 (0.04–0.09)	0.422	0–2

Table 2. Comparison of hematological parameters between kratom users and non-users. Adjusted for age, sex, BMI, current smoking, and current alcohol drinking.

leaves exhibited significantly lower levels of creatinine ($p = 0.004$), BUN ($p = 0.028$), and albumin ($p = 0.027$) compared to those with lower consumption. No significant differences were observed for other hematological or liver function parameters across the quartiles of use.

Sex-stratified analysis

Male participants (Table 6): In the male-only analysis, after adjusting for potential confounders, significant differences persisted in renal function markers. Male kratom users exhibited significantly lower creatinine levels ($p < 0.001$) and higher eGFR ($p < 0.001$) compared to male non-users. However, the previously observed differences in BUN and HbA1c were no longer statistically significant after adjustment.

Female participants (Table 7): After adjusting for potential confounders, the associations with renal function markers observed in males were not present. However, significant differences persisted for specific hematological and biochemical parameters. Female kratom users exhibited significantly lower Red Cell Distribution Width (RDW) ($p = 0.017$) and serum albumin levels ($p = 0.003$) compared to female non-users.

Discussion

In this large-scale, cross-sectional study conducted among a traditional kratom-using community in Southern Thailand, we found no evidence of clinically significant hematological or hepatic abnormalities associated with chronic kratom use after robust adjustment for confounding variables. However, our analysis revealed a complex and statistically significant association with markers of renal function and body composition, specifically lower serum creatinine, a consequently higher eGFR, and a lower BMI in kratom users. These findings challenge simplistic narratives of kratom's physiological effects and highlight the critical importance of accounting for lifestyle and demographic factors in evaluating its health impacts.

Our unadjusted data initially suggested numerous differences in hematological indices between users and non-users, a finding consistent with some previous reports that have noted minor alterations in blood parameters[11]. However, a key finding of our study is that these associations lost statistical significance after adjusting for covariates, most notably sex, BMI, and smoking status. This powerfully demonstrates that lifestyle and demographic factors, rather than kratom use itself, are likely the primary drivers of these previously observed hematological variations. This underscores the critical need for multivariable adjustment in observational studies of substance use, as failure to do so can lead to spurious conclusions.

Parameters	Unadjusted mean (SD)			Adjusted mean (95% CI)			Reference range
	Users	Non-users	*p*-value	Users	Non-users	*p*-value	
Glucose (mg/dL)	95.5 ± 32.4	96.6 ± 23.8	0.640	94.96 (91.41–98.51)	97.11 (93.64–100.58)	0.430	74–106
HbA1c (%)	5.5 ± 0.9	5.6 ± 1.0	0.401	5.57 (5.45–5.68)	5.57 (5.45–5.68)	0.979	3.8–5.6
BUN (mg/dL)	13.2 ± 4.0	13.4 ± 4.5	0.482	13.0 (12.5–13.4)	13.6 (13.1–14.1)	0.101	7–18
Creatinine (mg/dL) (Male)	0.88 ± 0.15	1.01 ± 0.35	< 0.001	0.89 (0.86–0.91)	0.99 (0.94–1.04)	< 0.001	0.67–1.17
Creatinine (mg/dL) (Female)	0.69 ± 0.13	0.70 ± 0.15	0.472	0.68 (0.63–0.73)	0.71 (0.68–0.73)	0.382	0.51–0.95
eGFR (mL/min/1.73 m)	94.7 ± 15.1	92.3 ± 18.2	0.088	95.42 (93.81–97.04)	91.55 (89.97–93.13	0.002	≥ 90
Total protein (g/dL)	8.1 ± 0.5	8.1 ± 0.4	0.117	8.11 (8.06–8.16	8.10 (8.05–8.15)	0.789	6.4–8.2
Albumin (serum) (g/dL)	3.70 ± 0.37	3.77 ± 0.31	0.008	3.71 (3.66–3.75)	3.76 (3.73–3.81)	0.055	3.4–5.0
Globulin (g/dL)	4.37 ± 0.47	4.35 ± 0.40	0.574	4.40 (4.45–4.56)	4.33 (4.27–4.38)	0.80	2.3–3.4
Total bilirubin (mg/dL)	0.53 ± 0.27	0.54 ± 0.25	0.536	0.52 (0.49–0.55)	0.55 (0.52–0.59)	0.136	0.20–1.00
Direct bilirubin (mg/dL)	0.13 ± 0.05	0.13 ± 0.05	0.119	0.13 (0.12–0.13)	0.13 (0.13–0.14)	0.367	0.0–0.2
AST (U/L)	26.87 ± 19.01	25.02 ± 16.16	0.205	25.66 (23.47–27.84)	26.19 (24.05–28.33)	0.749	15–37
ALT (U/L) (Male)	29.80 ± 16.85	33.44 ± 17.83	0.092	30.12 (27.91–32.33)	32.64 (29.07–36.21)	0.245	16–63
ALT (U/L) (Female)	25.40 ± 10.33	26.64 ± 28.31	0.736	25.08 (13.56–36.60)	25.88 (19.87–31.89)	0.909	14–59
Alk. Phosphatase (U/L)	76.72 ± 24.75	72.45 ± 19.50	0.022	75.58 (72.80–78.16)	73.55 (70.84–76.27)	0.342	46–116

Table 3. Comparison of clinical-chemistry parameters (liver and kidney function) between kratom users (n = 285) and non-users (n = 296). Adjusted for age, sex, BMI, current smoking, and current alcohol drinking.

Similarly, while some case reports have raised concerns about kratom-induced hepatotoxicity[12,13], our study found no significant differences in any liver enzyme markers (AST, ALT, ALP) or bilirubin levels between users and non-users in the adjusted analysis. Our findings align with other large-scale community-based studies in Malaysia, which also failed to detect significant liver injury in traditional, long-term users[14]. Furthermore, the general lack of adverse findings in our study is congruent with a prior report from this dataset which associated traditional kratom use with a favorable metabolic profile, including a reduced likelihood of metabolic syndrome[9], likely attributable to the combined effects of increased physical activity in this manual-laborer population and the potential appetite-suppressing properties of kratom alkaloids. This suggests that within the context of traditional use, the risk of overt liver damage may be low, and that previously reported cases of hepatotoxicity might be idiosyncratic reactions, related to adulterants, or result from non-traditional patterns of use[15].

A principal finding of this study is the association between kratom use and lower serum creatinine and higher eGFR, which persisted after multivariable adjustment. It is imperative to interpret this finding with caution. A conclusion of "improved kidney function" would be an over-interpretation of our cross-sectional data. Instead, we propose that the observed lower serum creatinine is likely attributable to differences in body composition.

Serum creatinine concentration is fundamentally a product of muscle metabolism, and directly proportional to muscle mass[16]. Although we did not directly measure lean body mass (e.g., via dual-energy X-ray absorptiometry), the kratom-using cohort had a significantly lower BMI compared to non-users. While BMI is not a perfect surrogate for muscle mass[17], it is reasonable to infer that the lower body mass in users correlates with reduced muscle mass, thereby resulting in lower baseline creatinine production. Consequently, the calculated higher eGFR likely reflects this physiological difference rather than a direct pharmacological enhancement of renal clearance by kratom. This observation is consistent with a previous analysis from this cohort[9]. While our analysis adjusted for BMI, we acknowledge that residual confounding from unmeasured differences in lean body mass may persist[18].

In our analysis utilizing self-reported consumption, we observed a significant dose-dependent relationship regarding renal function markers and serum protein. Specifically, higher consumption quantities were associated with progressively lower levels of creatinine, BUN, and albumin (Table 5). This inverse relationship aligns with the hypothesis of altered body composition or nutritional status in heavy users, given that BUN and albumin are sensitive markers of protein metabolism[19]. Conversely, we did not observe a linear dose–response relationship for the majority of other hematological or liver function biomarkers. This finding must be interpreted within the context of measurement limitations. The use of number of leaves as a unit of exposure is a semi-quantitative measure and lacks the precision of pharmacokinetic data (e.g., blood mitragynine concentrations). Variations in leaf size and alkaloid content, along with recall bias, introduce inherent noise to this variable[20]. Therefore,

Parameters	Duration of kratom use Estimated Marginal Means (EMM) ± Standard Error (SE)		*p*-value
	< 5 years (n = 50)	≥ 5 years (n = 235)	
WBC (10^3/μL)	7.75 ± 0.29	7.45 ± 0.19	0.378
RBC (10^6/ μL)	4.78 ± 0.08	4.80 ± 0.05	0.820
Hemoglobin (g/dL)	13.84 ± 0.21	13.84 ± 0.14	0.994
Hematocrit (%)	42.89 ± 0.59	42.86 ± 0.38	0.966
MCV (fL)	90.05 ± 1.13	89.76 ± 0.72	0.822
MCH (pg)	29.03 ± 0.44	28.98 ± 0.28	0.922
MCHC (g/dL)	32.17 ± 0.12	32.23 ± 0.08	0.634
RDW (%)	13.36 ± 0.23	13.26 ± 0.14	0.689
Platelets (10^3/μL)	274.57 ± 9.06	269.43 ± 5.75	0.618
Neutrophils (%)	52.53 ± 1.59	51.33 ± 1.01	0.508
Lymphocytes (%)	37.03 ± 1.50	38.62 ± 0.95	0.351
Monocytes (%)	5.83 ± 0.26	5.74 ± 0.16	0.749
Eosinophils (%)	4.53 ± 0.49	4.26 ± 0.31	0.617
Basophils (%)	0.78 ± 0.04	0.06 ± 0.02	0.663
Glucose (mg/dL)	111.24 ± 4.87	87.36 ± 3.09	< 0.001
HbA1c (%)	5.80 ± 0.13	5.44 ± 0.09	0.017
BUN (mg/dL)	13.11 ± 0.59	12.68 ± 0.37	0.518
Creatinine (mg/dL)	0.75 ± 0.02	0.76 ± 0.01	0.670
GFR (mL/min/1.73 m)	97.19 ± 1.75	96.90 ± 1.11	0.883
Total protein (g/dL)	8.16 ± 0.07	7.96 ± 0.04	0.023
Albumin (serum) (g/dL)	3.82 ± 0.06	3.61 ± 0.04	< 0.001
Globulin (g/dL)	4.34 ± 0.07	4.38 ± 0.05	0.662
Total bilirubin (mg/dL)	0.56 ± 0.04	0.46 ± 0.03	0.035
Direct bilirubin (mg/dL)	0.14 ± 0.01	0.12 ± 0.01	0.016
AST (U/L)	29.88 ± 2.89	29.12 ± 1.83	0.817
ALT (U/L)	29.11 ± 2.41	29.15 ± 1.53	0.988
Alk. Phosphatase (U/L)	80.11 ± 3.80	73.43 ± 2.41	0.123

Table 4. Comparison of key hematological and clinical-chemistry parameters among kratom users, stratified by duration of use, after adjustment for potential confounders. Adjusted by age, sex, BMI, current smoking, and current alcohol drinking. *p*-values were calculated using ANCOVA.

the absence of a statistical association for these other parameters does not definitively rule out dose-dependent physiological effects that might be detected with more precise exposure metrics. Nevertheless, even with these limitations, the observation that mean values for all groups remained within normal reference ranges, coupled with the lack of overt toxicity markers, provides reassurance regarding the safety profile of traditional use patterns.

We acknowledge the significant sex disparity between the user and control groups, which reflects the cultural demographics of traditional kratom use in this region. To address the potential for residual confounding by sex, we conducted sex-stratified analyses. Crucially, as shown in Table 6, the association with altered renal markers (lower creatinine and higher eGFR) remained highly statistically significant ($p < 0.001$) in the male-only cohort. This consistency demonstrates that the primary findings are not artifacts of sex imbalance in the total population, but represent robust associations within the principal user demographic.

Strengths

The present study has several notable strengths that enhance the validity of its findings. First, a key strength is the study's large sample size, recruited from a community of traditional kratom users in an endemic region of Southern Thailand. This provides a robust assessment of long-term, culturally integrated use, a context rarely captured in the existing literature. Second, the inclusion of a non-user control group from the same community, which was frequency-matched for age, minimizes potential confounding from demographic and environmental factors. Finally, a primary strength is our use of multivariable statistical models to adjust for a comprehensive set of crucial covariates, including sex, BMI, smoking, and alcohol consumption. This robust adjustment allowed for a nuanced interpretation of kratom's physiological correlates, distinguishing them from the effects of lifestyle factors.

Parameters	Daily quantity of use kratom leaves (n = 285) Estimated Marginal Means (EMM) ± Standard Error (SE)				*p*-value
	Q1 (< = 2 leaves) (n = 76)	Q2 (3–10 leaves) (n = 100)	Q3 (11–20 leaves) (n = 50)	Q4 (> = 20 leaves) (n = 59)	
WBC (10^3/μL)	7.56 ± 2.45	7.45 ± 2.37	7.64 ± 3.13	7.50 ± 3.05	0.946
RBC (10^6/ μL)	4.92 ± 0.06	4.73 ± 0.06	4.67 ± 0.08	4.72 ± 0.08	0.074
Hemoglobin (g/dL)	14.13 ± 0.18	13.77 ± 0.17	13.43 ± 0.22	13.64 ± 0.22	0.091
Hematocrit (%)	43.73 ± 0.49	42.64 ± 0.47	41.76 ± 0.62	42.18 ± 0.61	0.071
MCV (fL)	89.40 ± 0.94	90.37 ± 0.91	89.80 ± 1.21	89.90 ± 1.17	0.879
MCH (pg)	28.93 ± 0.36	29.15 ± 0.35	28.87 ± 0.47	29.06 ± 0.45	0.924
MCHC (g/dL)	32.27 ± 0.10	32.19 ± 0.10	32.08 ± 0.13	32.27 ± 0.13	0.566
RDW (%)	13.26 ± 0.19	13.37 ± 0.18	13.22 ± 0.24	13.25 ± 0.24	0.925
Platelets (10^3/μL)	269.44 ± 7.56	271.92 ± 7.32	272.16 ± 9.67	270.66 ± 9.42	0.994
Neutrophils (%)	52.36 ± 1.32	52.14 ± 1.28	49.96 ± 1.69	50.43 ± 1.65	0.528
Lymphocytes (%)	37.48 ± 1.24	37.59 ± 1.20	39.90 ± 1.59	39.72 ± 1.55	0.379
Monocytes (%)	5.93 ± 0.21	5.69 ± 0.21	5.43 ± 0.27	5.81 ± 0.27	0.482
Eosinophils (%)	4.17 ± 0.40	4.51 ± 0.39	4.65 ± 0.52	4.02 ± 0.50	0.679
Basophils (%)	0.07 ± 0.03	0.08 ± 0.03	0.07 ± 0.04	0.02 ± 0.04	0.623
Glucose (mg/dL)	95.86 ± 4.16	89.44 ± 4.03	99.57 ± 5.33	91.14 ± 5.19	0.264
HbA1c (%)	5.62 ± 0.11	5.53 ± 0.11	5.43 ± 0.14	5.41 ± 0.14	0.622
BUN (mg/dL)	13.53 ± 0.48	12.72 ± 0.46	12.37 ± 0.61	11.34 ± 0.60	0.028
Creatinine (mg/dL)	0.78 ± 0.02	0.77 ± 0.02	0.72 ± 0.02	0.70 ± 0.02	0.004
GFR (mL/min/1.73 m)	94.93 ± 1.44	96.75 ± 1.39	100.07 ± 1.84	99.95 ± 1.79	0.059
Total protein (g/dL)	8.08 ± 0.06	7.99 ± 8.06	8.05 ± 0.07	7.98 ± 0.07	0.490
Albumin (serum) (g/dL)	3.77 ± 0.05	3.67 ± 0.04	3.59 ± 0.06	3.59 ± 0.06	0.027
Globulin (g/dL)	4.31 ± 0.06	4.38 ± 0.06	0.46 ± 0.08	4.39 ± 0.07	0.481
Total bilirubin (mg/dL)	0.54 ± 0.03	0.48 ± 0.03	0.42 ± 0.04	0.45 ± 0.04	0.173
Direct bilirubin (mg/dL)	0.13 ± 0.01	0.13 ± 0.01	0.12 ± 0.01	0.14 ± 0.01	0.164
AST (U/L)	28.74 ± 2.40	28.51 ± 2.32	29.64 ± 3.07	32.57 ± 2.99	0.610
ALT (U/L)	28.95 ± 2.01	29.54 ± 1.94	29.52 ± 2.57	28.30 ± 2.50	0.965
Alk. Phosphatase (U/L)	77.03 ± 3.18	73.34 ± 3.08	75.93 ± 4.07	73.54 ± 3.96	0.788

Table 5. Key hematological and clinical-chemistry parameters among kratom users, stratified by daily quantity of use. Adjusted by age, sex, BMI, current smoking, and current alcohol drinking. *p*-values were calculated using ANCOVA.

Limitations

First, the primary limitation is the cross-sectional design, which, by its nature, captures exposure and outcome data at a single point in time and fundamentally precludes the establishment of a temporal sequence or definitive causal inference. Second, data on the duration and quantity of kratom use were based on self-reports, which may be subject to recall bias. Third, although our statistical models adjusted for crucial confounders, the potential for residual and unmeasured confounding remains. Fourth, the small sample size of female kratom users (n = 61) limits the statistical power and generalizability of the sex-stratified findings. Fifth, we did not directly measure lean body mass. Although BMI was used as a proxy for body size, it may not perfectly reflect muscle mass, limiting our ability to definitively attribute low creatinine levels solely to reduced muscle mass. Finally, the kratom products consumed by participants were not chemically analyzed, so variations in alkaloid potency or the presence of adulterants could not be assessed. Furthermore, we lacked pharmacokinetic data (e.g., blood mitragynine concentrations) to corroborate self-reported usage, which limits the precision of our dose–response analysis.

Conclusion

In conclusion, this study provides compelling evidence that in a real-world, traditional-use setting, chronic kratom consumption is not associated with clinically significant hepatic or hematological toxicity after accounting for crucial confounding factors. The observed association with altered renal markers is most plausibly explained by differences in body composition rather than a direct effect on kidney function. Our findings provide a nuanced perspective on the safety profile of traditional kratom use, suggesting the physiological impact is more subtle and multifaceted than previously reported. Prospective, longitudinal studies are urgently needed to confirm these findings and to delineate the true, long-term causal impact of kratom on renal and metabolic health.

Parameters	Male Kratom users (n = 224)	Male Non kratom users (n = 88)	*p*-value	Reference range
WBC (10^3/μL)	8.11 ± 0.16	7.93 ± 0.24	0.518	4–9
RBC (10^6/ μL)	5.03 ± 0.04	5.00 ± 0.06	0.691	3.8–5.3
Hemoglobin (g/dL)	14.64 ± 0.10	14.67 ± 0.16	0.875	14–18
Hematocrit (%)	45.14 ± 0.29	45.12 ± 0.44	0.963	42–52
MCV (fL)	90.26 ± 0.53	90.92 ± 0.81	0.479	80–100
MCH (pg)	29.29 ± 0.20	29.55 ± 0.31	0.448	28–32
MCHC (g/dL)	32.41 ± 0.05	32.49 ± 0.08	0.404	31–35
RDW (%)	13.31 ± 0.10	13.19 ± 0.16	0.504	10.0–16.5
Platelets (10^3/μL)	259.19 ± 4.25	252.12 ± 6.45	0.344	150–350
Neutrophils (%)	52.66 ± 0.78	53.79 ± 1.18	0.409	42–85
Lymphocytes (%)	36.59 ± 0.73	35.49 ± 1.10	0.391	11–49
Monocytes (%)	5.90 ± 0.13	5.89 ± 0.19	0.959	0–9
Eosinophils (%)	4.81 ± 0.24	5.75 ± 0.37	0.883	0–6
Basophils (%)	0.05 ± 0.02	0.09 ± 0.03	0.210	0–2
Glucose (mg/dL)	96.18 ± 2.37	99.10 ± 3.59	0.482	74–106
HbA1c (%)	5.52 ± 0.07	5.70 ± 0.11	0.143	3.8–5.6
BUN (mg/dL)	13.85 ± 0.32	14.54 ± 4.82	0.220	7–18
Creatinine (mg/dL)	0.88 ± 0.02	0.99 ± 0.02	< 0.001	0.67–1.17
GFR (mL/min/1.73 m)	93.40 ± 0.96	87.79 ± 1.46	< 0.001	≥ 90
Total protein (g/dL)	8.07 ± 0.03	8.01 ± 0.05	0.223	6.4–8.2
Albumin (serum) (g/dL)	3.72 ± 0.03	3.72 ± 0.04	0.901	3.4–5.0
Globulin (g/dL)	4.35 ± 0.04	4.29 ± 0.05	0.324	2.3–3.4
Total bilirubin (mg/dL)	0.57 ± 0.02	0.60 ± 0.03	0.502	0.20–1.00
Direct bilirubin (mg/dL)	0.14 ± 0.004	0.15 ± 0.01	0.498	0.0–0.2
AST (U/L)	29.93 ± 1.42	31.13 ± 2.15	0.631	15–37
ALT (U/L)	32.05 ± 1.23	34.56 ± 1.87	0.245	16–63
Alk. Phosphatase (U/L)	77.49 ± 1.76	73.95 ± 2.67	0.253	46–116

Table 6. Comparison of hematological and clinical-chemistry parameters between male kratom users and male non-users. Adjusted for age, BMI, current smoking, and current alcohol drinking. *p*-values were calculated using ANCOVA.

Parameters	Female Kratom users (n = 61)	Female Non kratom users (n = 208)	*p*-value	Reference range
WBC (10^3/μL)	6.68 ± 0.57	6.94 ± 0.57	0.332	4–9
RBC (10^6/ μL)	4.71 ± 0.15	4.65 ± 0.15	0.361	3.8–5.3
Hemoglobin (g/dL)	12.34 ± 0.45	12.39 ± 0.45	0.239	12–16
Hematocrit (%)	39.76 ± 1.23	39.20 ± 1.23	0.328	36–48
MCV (fL)	84.48 ± 2.76	84.49 ± 2.74	0.997	80–100
MCH (pg)	26.83 ± 1.05	26.72 ± 1.05	0.822	28–32
MCHC (g/dL)	31.62 ± 0.31	31.48 ± 0.31	0.317	31–35
RDW (%)	13.75 ± 0.48	14.28 ± 0.48	0.017	10.0–16.5
Platelets (10^3/μL)	281.71 ± 20.12	285.30 ± 20.04	0.699	150–350
Neutrophils (%)	47.03 ± 3.13	347.72 ± 3.12	0.636	42–85
Lymphocytes (%)	39.34 ± 2.92	38.04 ± 2.90	0.330	11–49
Monocytes (%)	6.39 ± 0.48	6.70 ± 0.48	0.161	0–9
Eosinophils (%)	7.10 ± 1.03	7.43 ± 1.03	0.485	0–6
Basophils (%)	0.13 ± 0.06	0.12 ± 0.06	0.524	0–2
Glucose (mg/dL)	80.41 ± 7.27	80.74 ± 7.24	0.921	74–106
HbA1c (%)	5.40 ± 0.27	5.14 ± 0.27	0.060	3.8–5.6
BUN (mg/dL)	10.96 ± 1.18	11.44 ± 1.18	0.377	7–18
Creatinine (mg/dL)	0.71 ± 0.05	0.73 ± 0.05	0.355	0.51–0.95
GFR (mL/min/1.73 m)	95.26 ± 3.95	93.41 ± 3.94	0.310	≥ 90
Total protein (g/dL)	7.77 ± 0.13	7.83 ± 0.13	0.357	6.4–8.2
Albumin (serum) (g/dL)	3.34 ± 0.10	3.48 ± 0.10	0.003	3.4–5.0
Globulin (g/dL)	4.43 ± 0.12	4.35 ± 0.12	0.122	2.3–3.4
Total bilirubin (mg/dL)	0.37 ± 0.07	0.43 ± 0.07	0.074	0.20–1.00
Direct bilirubin (mg/dL)	0.10 ± 0.01	0.11 ± 0.01	0.481	0.0–0.2
AST (U/L)	19.99 ± 4.73	19.92 ± 4.71	0.975	15–37
ALT (U/L)	19.81 ± 8.25	20.46 ± 8.22	0.863	14–59
Alk. Phosphatase (U/L)	75.23 ± 6.26	75.78 ± 6.23	0.984	46–116

Table 7. Comparison of hematological and clinical-chemistry parameters between female kratom users and female non-users. Adjusted for age, BMI, current smoking, and current alcohol drinking. *p*-values were calculated using ANCOVA.

Data availability

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants. Data may be made available from the corresponding author upon reasonable request.

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Declaration of generative AI and AI-assisted technologies in the writing process
During the preparation of this work the authors used Gemini (Google) in order to refine language, improve sentence structure, and ensure clarity and consistency in the scientific narrative. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Author contributions
Aroon La-up: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Resources, Writing—original draft, Writing—review & editing. Udomsak Saengow: Conceptualization, Methodology, Investigation, Validation, Writing—review & editing. Apinun Aramrattana: Conceptualization, Methodology, Supervision, Resources, Writing—review & editing.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval
The study protocol was reviewed and approved by the Institutional Review Board of Walailak University. The protocol number: WU-EC-AH-2-144-63. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all participants before data collection.

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