ORIGINAL ARTICLE

Long-Term Effects of Kratom (*Mitragyna speciosa*) Use

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ABSTRACT

Introduction: Kratom or (*Mitragyna speciosa*) leaves are consumed as a folk remedy and opioid substitute in the Southeast Asian region. There is still a lack of information about the long-term or toxic-causing effects of kratom use. **Methods:** A total of thirteen regular kratom users, with long-term (>20 twenty years) kratom use history were recruited for this cross-sectional pilot study. Respondents were required to undergo a blood-test and laboratory anaysis was conducted to determine the *mitragynine* content in an acquired street sample of kratom. **Results:** The regular, long-term consumption of brewed kratom decoction did not cause any significant alterations in haematological, kidney, liver, thyroid, inflammatory and gastrointestinal analytes in a cohort of kratom users who had no history of substance misuse. However, those who had a higher intake (>3 glasses per day) of kratom exhibited higher lipid values (except for HDL-cholesterol), and a moderate elevation of homocysteine level. **Conclusion:** Long-term (>20 years with a daily intake of ≥87.54mg of *mitragynine*) kratom consumption was not associated with altered biochemical levels, although prolonged and heavy use (>3 glasses daily) may result in cardiovascular risks. The latter finding, however, requires further investigation.

Keywords: *Mitragynine*, Kratom, Toxicity, Haematology, Cardiotoxicity

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INTRODUCTION

Kratom (*Mitragyna speciosa*) leaves are widely used in rural Southeast Asia for its therapeutic value (1). Rural folks traditionally use kratom to treat common health disorders (e.g. cough, hypertension, diabetes, and pain), while manual labourers rely on kratom to enhance work productivity (1). Since kratom is believed to have pain suppressing effects, it is also used as a safe alternative to opioids (1, 2), since its most abundant alkaloid, *mitragynine* has been shown to bind to opioid-receptors (2, 3). Over the last decade, kratom has gained ground in the US, chiefly because of its potential to reduce pain, relieve opioid withdrawal pains, and aid in alleviating psychological problems like anxiety and depression (2). Its principal psychoactive alkaloids, both *mitragynine* and *7-hydroxymitragynine*, were reported to have an effect on opioid receptors (3). In the West, kratom consumption is being seen as a public health threat on account of several kratom toxicity cases triggered primarily in those who use kratom in combination with other substances like ethanol, benzodiazepines, narcotics and pain-relieving medication (acetaminophen) (4, 5). It is unclear if *mitragynine*/kratom *per se* was responsible for the these adverse health occurrences, or if they were caused by the concomitant use of kratom with other illicit drugs (5), or the consumption of unreliable kratom products with a higher *7-hydroxymitragynine* content than is found naturally (6).

Due to the increase in kratom-related health emergencies (5), the US Food and Drug Administration (FDA) has expressed concern about the unapproved sales and distribution of a variety of kratom products. It is pressing the government to regulate kratom and its alkaloids in the US under the Control Substances Act (CSA). Although kratom remains legal at the Federal level, issues related to kratom poisoning (e.g. toxicities and deaths) continue to unfold in the US and are reported to evolve from the use of kratom products, primarily *mitragynine* and *7-hydroxymitragynine* (7). The latest information from the US National Poison Data System (NPDS) indicates that there were about 1807 kratom exposure cases

reported between 2011 and 2017 (5). In fact, two-thirds (65%) of the exposure cases occurred between 2016 to 2017, while 51.9% of the exposure incidents were associated with various adverse medical outcomes such as seizures, respiratory depression, cardiac arrest, renal failure, etc. (5).

Based on the available findings, it can be hypothesised that kratom users in US, specifically those who co-used kratom with other illicit substances and alcohol, have higher possibility of experiencing adverse, but not life-threatening, health problems (4, 5, 7). Findings from an animal study indicated that higher *mitragynine* administration has the potential to alter haematological and biochemical parameters (8). Several studies have also highlighted kratom's (*mitragynine*) association with biochemical alterations indicative of liver injuries, neonatal withdrawal symptoms, kratom dependence and withdrawal, overdose, gastrointestinal and cardiovascular (e.g. bradycardia, tachycardia, palpitation, etc.) problems (4, 5, 7, 9, 10, 11). Researchers believe that most of the mortality incidents in the West were caused by the toxic effect of combining illicit substances with kratom (7), or due to the combination of kratom with conventional drugs that resulted in lethal herb-drug interactions (12). About 95% of those who have passed away from kratom use had current drug abuse histories (7).

The present study examines respondents who have a much longer history of kratom use— more than 20 years, as compared to a previously studied group consisting of those who used kratom for between two and eleven years (13). Furthermore, we also analysed cardiovascular and gastric cancer markers. Given the unavailability of safety data on the long-term effects of kratom use, this study seeks to shed light on whether prolonged kratom use (>20 years) was associated with adverse health effects.

MATERIALS AND METHODS

Study design, inclusion and exclusion criteria and measure

Thirteen kratom users consented to participate in this cross-sectional study. All the respondents were recruited through purposive sampling from the northern state of Penang. Rural dwellers in this state still maintain their traditional kratom using habit. Respondents in this study only used brewed kratom juice, which is commonly obtained from illegal kratom suppliers in the community. None of the respondents have chewed or smoked kratom before. Respondents were eligible to participate in the study if they were; 1) below 55 years of age, and 2) have more than 20 years regular kratom use history. We recruited those who were less than 55 years of age since older respondents may be exposed to unrelated health risks. We excluded those who had current or previous alcohol and drug use history. All the study data were collected from January 2019 to March 2019. A trained research officer conducted the interviews using a semi-structured questionnaire that collected information on the respondent's demographic characteristics (e.g. ethnicity, current age, marital status, etc.), and kratom use history (e.g. duration of kratom use, first age of kratom use, etc.). Moreover, respondents were also asked to share the negative experiences, and any health problems they encountered in the course of their kratom use. We also measured the body mass index (BMI) of each respondent, recorded their daily caloric food intake, and documented their history of cigarette smoking. This study was approved by the Human Ethics and Research Committee of Universiti Sains Malaysia (USM) (USM/JEPeM/19040224). Respondents were compensated with RM50 (USD=13.5) for their participation. All gave their written informed consent.

Haematological and biochemical analyses

Blood samples were analysed at a diagnostic laboratory (PATHLAB, Malaysia). Details of the haematological and biochemical analysis have been described in a previous study (13). Additional tests included prothrombin time and International Normalised Ratio (INR), cystatin C, homocysteine, hs-C reactive protein (hsCRP), creatine phosphokinase, apolipoproteins A1, B and Apo B/Apo A1 ratio. The cancer antigen 19.9 (CA 19.9) test was also done to screen for gastric cancer marker.

Study analysis

All the study data were analysed with the Statistical Package for Social Sciences (SPSS) version 24. Descriptive statistics were used to describe the sociodemographic characteristics and kratom use histories of respondents. The haematological and biochemical parameters of respondents, and the mean scores and standard deviations (SD) were calculated to compare with the reference range scores. Independent t-test were computed to determine the mean differences in the biochemical parameters between respondents who consumed $\leq$3 glasses (low quantity) and >3 glasses (high quantity) of kratom juice per day. We chose to study the relationship between the low and high dose effects of kratom use because higher quantities of kratom use were reported to cause adverse health effects (1). The statistical significance for all tests was set at $p<0.05$.

Kratom juice analysis

Reagents and chemicals

Methanol (HPLC grade) was purchased from Merck (Germany). Mitragynine was extracted from Mitragyna speciosa leaves following the method described by Sharma et al. (2019) (14). The chemical structure and purity of mitragynine was confirmed by 1H & 13C NMR, MS and HPLC-UV (14).

Sample collection and preparation

In traditional settings, kratom traders typically use fresh and matured kratom (Mitragyna speciosa) leaves to produce kratom juice for local consumption. Unlike in the US where users have a liking for using red and

green-veined kratom powder, local kratom traders usually combine both the green and red-veined leaves to prepare kratom juice. On average, respondents in this study consumed about three packets of kratom decoction daily (approximately 1,120 mL). It was previously shown that the major alkaloid detected in local kratom tea/juice was mitragynine, followed by paynantheine, speciogynine and speciociliatine (13). Mitragynine is the major psychoactive alkaloid of kratom. To estimate the amount of mitragynine consumed by our respondents, we purchased a sample packet of street kratom. The acquired sample was measured and freeze-dried to evaporate off the water content. The alkaloid content of the lyophilized powder was then pre-concentrated with methanol prior to GC-MS analyses (13).

Quantification of mitragynine content using a validated GC-SIM-MS method

Mitragynine content of the acquired kratom juice/tea (methanol extract, 20 mg/mL) was estimated using a validated gas chromatography-mass spectrometry (GC-MS) method with a selective ion monitoring (SIM) mode as described in a previous study (13). Detection of mitragynine (kratom juice) was done by comparing the retention time (16.8 min) and the major product ion (m/z 214) of the analyte with that of mitragynine standard (> 98% purity) (Figure 1).

RESULTS

The demographic characteristics and kratom use history of respondents

The demographic characteristics and kratom use history of respondents are shown in Table I. The sample consisted only of Malay males (100%, n=13/13). The mean age of respondents was 45.1 years. The majority were married (85%, n=11/13), and had completed upper secondary education (69%, n=9/13). None were unemployed. The mean age of first kratom use was 27.5 years (SD=4.2), and their mean duration of kratom use was 20.4 years. Respondents consumed, on average, 4 glasses of kratom juice daily (Table I). Forty-six percent (n=6/13) consumed >3 glasses of kratom juice daily, while 54% (n=7/13) used ≤3 glasses of kratom per day. The mean BMI of the respondents were 27.2 (SD=4.5), and their mean intake of daily calories was 2,084.7 (SD=320.6). Almost all (n=12/13) had current history of cigarette smoking, and their mean duration of smoking was 26.6 years (SD=2.4).

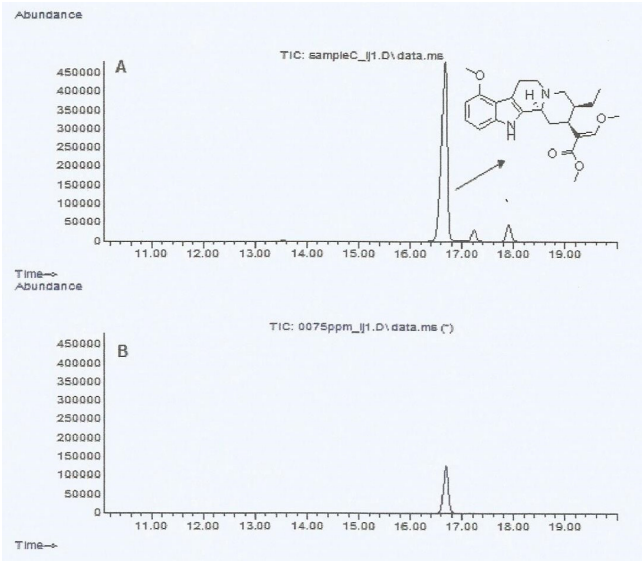

Figure 1: (A) GC-SIM-MS chromatogram of the purchased kratom juice sample (methanol extract); (B) GC-SIM-MS chromatogram of mitragynine standard (75 µg/mL).

Haematology blood test findings

There were no significant alterations in the haematology parameters of the respondents. Only subtle alterations were observed for RDW value and prothrombin time as shown in Table I.

Table I: Respondents socio-demographic characteristics and kratom use history

	n (%)
Gender Male	13 (100)
Ethnicity Malay	13 (100)
Mean age	45.1 years (SD=6.6)
Marriage Single Married	 2 (15) 11 (85)
Education 9 years ≥11 years	 4 (31) 9 (69)
Employment Employed	 13 (100)
Kratom use history	
Mean age of first kratom use	27.5 years (SD=4.2)
Mean duration of kratom use	20.4 years (SD=0.7)
Mean frequency of daily kratom use	5.6 times (SD=2.4)
Mean quantity of daily kratom use	4 glasses (SD=2.5)
Daily quantity of kratom use ≤3 glasses >3 glasses	 7 (54) 6 (46)
Mean BMI	27.2 (SD=4.5)
Mean calories daily	2084.7 calories (SD=320.6)
Mean smoking duration	26.6 years (SD=2.4)
Smoker Yes No	 12 (92) 1 (8)
Health problems since kratom use No	 13 (100)
Blood group O RH AB RH A RH B RH	 7 (54) 1 (8) 2 (15) 3 (23)

Biochemical test findings

Results from the blood chemistry analyses indicated that there were no significant alterations in the kidney, liver or thyroid functions, rheumatoid factor, and CA 19.9 level (Table II). However, the lipid profile and apolipoprotein parameters were found to be altered. It was apparent that the level of total cholesterol, LDL, triglycerides, hs-CRP and homocysteine levels were higher than the reference range, although the HDL remained at the normal range (Table II).

Differences in the haematology and bio-chemical parameters between those who consumed lower (≤3 glasses) and higher (>3 glasses) quantity of kratom juice

It has been reported that those who consumed kratom regularly over prolonged periods may experience weight loss, decreased appetite and libido, fatigue, etc. (1). Therefore, we investigated the dose-response effects of kratom use on haematological and biochemical parameters. Since chronic kratom use was associated with gastrointestinal discomfort and elevation in lipid profile (13), we attempted to determine whether higher intake of kratom was associated with altered haematological and biochemical parameters. We found there was a significant increase beyond the reference range particularly for RDW and prothrombin time among those who consumed ≤3 glasses of kratom per day, relative to those who consumed >3 glasses of kratom (Table III). However, there were no significant alterations in the kidney parameters of the respondents, except for the cystatin value which appeared higher than the reference range among those who consumed >3 glasses of kratom juice per day. No significant changes in the glucose, liver function, thyroid function and CA 19.9 levels were detected between those who reported consuming more than or less than 3 glasses per day. However, our results indicated that respondents who consumed >3 glasses of kratom on a regular basis had substantial elevations in total cholesterol, LDL, Apo B, Apo B/A1 ratio when compared to the individual reference range parameters. There were also elevations in homocysteine and triglyceride levels, but interestingly the values turn out to be high among those who reported consuming lower (≤3 glasses) quantity of daily kratom use. However, hs-CRP was above the reference range for both groups.

Estimation of mitragynine content in the kratom sample

In this study, approximately 360 mL of kratom tea/juice was lyophilized to yield 4.39 g of water extract and subsequently extracted with methanol to yield 3.1 g of methanolic extract. Based on GC-SIM-MS quantification, the mitragynine content in the methanol extract (20 mg/mL) was 0.1883 ± 0.01 mg/mL which is equivalent to 29.18 mg in 3.1 g of methanol extract (0.94% (w/w)). The mitragynine content in the street sample was found to be around 29.18 mg per glass (360mL of kratom tea/juice). It can, therefore, be inferred that the respondents ingested approximately 87.54 mg of mitragynine per

Table II: Respondents biochemical profile.

	Scores (n=13) Mean ± (SD)	Unit	Reference Range
	Haematology		
ESR	7.5 (4.2)	MM/HR	0-10
RBC	5.5 (.74)	X10^12/L	4.5-6.5
Haemoglobin	15.1 (.94)	G/DL	13.0-18.0
PCV (HCT)	41.6 (11.4)	%	40-54
MCV	82.5 (10.1)	FL	76-96
MCH	27.8 (3.4)	PG	27-32
MCHC	33.8 (.90)	G/DL	32-36
RDW value	**15.0 (1.9)***	%	11.5-14.5
Platelet count	326.6 (74.4)	X10^9/L	150-400
WBC	9.8 (2.5)	X10^/L	4.0-11.0
	Differential count		
Neutrophil	50.2 (9.5)	%	40-75
Lymphocyte	36.1 (7.7)	%	20-45
Monocyte	8.6 (2.4)	%	2-10
Eosinophil	4.9 (3.2)	%	0-6
Basophil	0.31 (.48)	%	0-2
	Prothrombin time		
Patient time	**14.4 (2.9)***	Seconds	9.8-12.1
Control time	14.0 (.00)	Seconds	
INR	1.1 (.13)		
	Diabetes screen		
Glucose	5.6 (1.4)	mmol/L	Fasting 3.9-5.6
	Kidney function test		
Urea	2.9 (.81)	mmol/L	1.7-8.4
Creatinine	87.5 (10.5)	mmol/L	62-115
Calcium	2.3 (.09)	mmol/L	2.12-2.52
Inorganic phosphate	1.3 (.26)	mmol/L	0.78-1.65
Uric acid	0.38 (.10)	mmol/L	0.20-0.42
Sodium	145.4 (2.3)	mmol/L	137-150
Potassium	4.5 (.36)	mmol/L	3.5-5.3
Chloride	101.4 (1.6)	mmol/L	96-108
Cystatin C	**0.97 (.16)***	mg/L	0.50-0.96
	Microalbumin		
Urine microalbumin	6.70 (5.0)	mg/L	
Urine creatinine	11.5 (7.1)	nmol/L	
Microalb: creat ratio	0.76 (1.2)	mg/MMOL	<3.4
	Lipid profile		
Total cholesterol	**5.8 (1.1)***	mmol/L	<5.2
HDL	**1.3 (.25)***	mmol/L	>1.04
LDL	**3.6 (.91)***	mmol/L	<2.6
Triglycerides	**2.2 (1.8)***	mmol/L	<1.7
Total/HDL ratio	4.6 (1.4)		<5.0
Hs-C reactive protein	**5.3 (3.3)***	mg/L	<4.7
	Apolipoproteins		
Apolipoprotein A1	1.3 (.17)	g/L	0.94-1.78
Apolipoprotein B	1.3 (.25)	g/L	0.63-1.33
Apo B/APO A1 ratio	1.0 (.25)		<1.00
Homocysteine	**19.2 (13.8)***	µmol/L	5.0-15.0
	Liver function test		
Total protein	75.2 (3.7)	g/L	64-83
Albumin	41.5 (3.3)	g/L	30-50
Globulin	33.7 (4.1)	g/L	20-50
A/G ratio	1.3 (.23)		1.2-2.5
Total bilirubin	9.5 (2.10)	µmol/L	<17
Alkaline phosphatase	89.6 (12.7)	IU/L	39-117
SGOT (AST)	30.6 (6.2)	IU/L	0-40
SGPT (ALT)	28.1 (10.1)	IU/L	0-53
GGT	40.3 (14.8)	IU/L	<73
CPK (Total)	162.9 (76.6)	U/L	39-308
	Thyroid screen		
Thyroxine (T4)	111.4 (29.8)	nmol/L	64.0-167.0
Rheumatoid factor	17.3 (25.6)	IU/ML	0-35
	Tumour marker		
CA 19.9	9.4 (5.7)	U/ML	<37.0

*Denotes values are higher than the reference range.

Table III: Differences in the biochemical parameters of between those who consumed ≤3 glasses and >3 glasses of kratom daily

	≤3 glasses (n=7) Mean ± (SD)	>3 glasses (n=6) Mean ± (SD)	Difference	*t*	df	*P*-value	Reference Range
			Haematology				
ESR	7.1 (4.3)	8.0 (4.6)	0.9	0.349	11	0.782	0-10
RBC	**5.5 (1.03)***	5.4 (.23)	0.1	0.072	11	**0.014**	4.5-6.5
Haemoglobin	14.5 (.72)	15.8 (.63)	1.3	3.455	11	0.863	13.0-18.0
PCV (HCT)	37.5 (14.6)	46.3 (2.2)	8.8	1.455	11	0.105	40-54
MCV	80.9 (13.3)	**84.5 (4.9)***	3.6	0.630	11	**0.031**	76-96
MCH	27.0 (4.5)	**28.8 (1.2)***	1.8	0.963	11	**0.008**	27-32
MCHC	33.4 (.98)	34.3 (.52)	0.9	2.032	11	0.153	32-36
RDW value	**15.4 (2.6)***	14.6 (.82)	0.8	0.726	11	**0.012**	11.5-14.5
Platelet count	356.4 (69.8)	291.8 (68.7)	64.6	1.675	11	0.576	150-400
WBC	9.10 (2.4)	9.7 (2.7)	0.6	0.215	11	0.911	4.0-11.0
			Differential count				
Neutrophil	49.0 (10.20)	51.5 (9.30)	2.5	0.459	11	0.894	40-75
Lymphocyte	36.9 (9.0)	35.2 (6.6)	1.7	0.380	11	0.702	20-45
Monocyte	10.3 (1.5)	6.7 (1.8)	3.6	4.023	11	0.545	2-10
Eosinophil	3.7 (1.7)	**6.2 (4.2)***	2.5	1.432	11	**0.012**	0-6
Basophil	.14 (.38)	**.50 (.55)***	0.36	1.387	11	**0.042**	0-2
			Prothrombin time				
Patient time	15.5 (3.20)**	13.1 (1.10)**	2.4	1.554	11	0.166	9.8-12.1
Control time	14.0 (.00)	14.00 (.00)	0				
INR	1.1 (.2)	**1.0 (.1)***	0.1	1.683	11	**0.000**	
			Diabetes screen				
Glucose	5.6 (1.9)	5.6 (.70)	0	0.000	11	0.106	Fasting 3.9-5.6
			Kidney function test				
Urea	3.2 (.93)	2.6 (.60)	0.6	1.259	11	0.195	1.7-8.4
Creatinine	84.0 (10.1)	91.5 (10.4)	7.5	1.316	11	0.886	62-115
Calcium	2.24 (.10)	**2.30 (.12)***	0.06	0.900	11	**0.044**	2.12-2.52
Inorganic phosphate	1.3 (.30)	1.3 (.30)	0	0.043	11	0.967	0.78-1.65
Uric acid	.40 (.10)	.40 (.10)	0	0.759	11	0.916	0.20-0.42
Sodium	144.7 (2.6)	146.2 (1.6)	1.5	1.175	11	0.448	137-150
Potassium	4.50 (.27)	4.60 (.47)	0.1	0.555	11	0.167	3.5-5.3
Chloride	101.14 (2.1)	101.7 (.8)	0.56	0.568	11	0.315	96-108
Cystatin C	0.88 (.14)	1.1 (.13)**	0.22	2.399	11	0.972	0.50-0.96
			Microalbumin				
Urine microalbumin	8.3 (5.2)	4.9 (4.4)	3.4	1.251	11	0.757	
Urine creatinine	12.8 (6.4)	10.0 (8.1)	2.8	0.704	11	0.502	
Microalb: create ratio	1.03 (1.6)	0.45 (.24)	0.58	0.879	11	0.109	<3.4
			Lipid profile				
Total cholesterol	5.3 (.89)**	6.5 (1.0)**	1.2	2.247	11	0.839	<5.2
HDL	1.3 (.31)**	1.3 (.18)**	0	0.005	11	0.353	>1.04
LDL	3.1 (.80)**	4.1 (.82)**	1	1.833	11	0.893	<2.6
Triglycerides	2.2 (2.2)**	1.2 (1.5)	1	0.056	11	0.196	<1.7
Total/HDL ratio	4.2 (1.4)	5.1 (1.3)	0.9	1.110	11	0.860	<5.0
Hs-C reactive protein	5.3 (3.4)**	5.2 (3.6)**	0.1	0.044	11	0.847	<4.7
			Apolipoproteins				
Apolipoprotein A1	1.30 (.20)	1.30 (.15)	0	0.217	11	0.661	0.94-1.78
Apolipoprotein B	1.14 (.20)	1.41 (.24)**	0.27	2.201	11	0.878	0.63-1.33
Apo B/APO A1 ratio	.90 (.20)	1.12 (.30)**	0.22	1.851	11	0.158	<1.00
Homocysteine	21.2 (18.2)**	16.4 (3.7)**	4.8	0.572	11	0.119	5.0-15.0
			Liver function test				
Total protein	75.0 (3.8)	75.3 (3.10)	0.3	0.154	11	0.900	64-83
Albumin	43.1 (3.4)	39.5 (1.6)	3.6	2.364	11	0.236	30-50
Globulin	31.9 (3.3)	35.8 (4.0)	3.9	1.950	11	0.603	20-50
A/G ratio	1.4 (.22)	1.1 (.16)	0.3	2.198	11	0.325	1.2-2.5
Total bilirubin	10.4 (2.5)	8.5 (3.4)	1.9	1.178	11	0.475	<17
Alkaline phosphatase	87.4 (14.1)	92.7 (11.40)	5.3	0.729	11	0.608	39-117
SGOT (AST)	33.6 (4.2)	27.2 (6.7)	6.4	2.106	11	0.144	0-40
SGPT (ALT)	33.0 (11.60)	22.3 (3.5)	10.7	2.159	11	0.078	0-53
GGT	41.6 (17.3)	38.8 (12.7)	2.8	0.320	11	0.465	<73
CPK (Total)	173.7 (75.30)	150.2 (83.1)	23.5	0.536	11	0.545	39-308
			Thyroid screen				
Thyroxine (T4)	120.5 (24.4)	100.7 (34.1)	19.8	1.218	11	0.093	64.0-167.0
Rheumatoid factor	22.0 (33.7)	11.8 (11.7)	10.2	0.699	11	0.101	0-35
			Tumour marker				
CA 19.9	7.5 (4.4)	11.3 (6.7)	3.8	1.175	11	0.210	<37.0

*Denotes differences between those who consumed ≤3 or >3 glasses of kratom daily at ($p<0.05$).
**Denotes values are higher than the reference range.

day, corresponding to an average of three glasses of kratom juice.

DISCUSSION

Although kratom leaves have customarily been used for its broad therapeutic values such as relieving pain, elevating mood, and as an affordable substitute for opioids in Southeast Asia, several studies from the West have emerged linking kratom consumption with poisoning and death (4, 5, 7). Kratom use for the self-treatment of pain first was identified in the US in 2007 (1). Subsequently large scale surveys have shown that kratom was being used to self-treat chronic pain, opioid withdrawal and dependence, as well as psychological problems (1, 2). Despite this, the FDA has kept alleging that kratom's main alkaloids, mitragynine and 7-hydroxymitragynine, had a role in the majority of kratom fatalities in the US (7). In fact, the link between mitragynine and the reported death rates has been poorly elucidated, since 71% of the fatalities were reported as accidental (including misadventure), while 9% were classified as intentional (suicide) (7). A recent study estimated that the risk of overdose death is >1000 times greater for opioids than for kratom (15). In fact, the majority who have encountered adverse health problems were those who had current histories of drug use problem, chiefly opioid abuse (7, 15). Meanwhile, in Southeast Asia, traditional kratom use has, thus far, not been associated with any major health concerns, although it has been placed under the Poisons Act 1952 in Malaysia (1). While previous studies have documented the side-effects of kratom, and its use as an opioid substitute among heroin users in Malaysia (1), the safety of long-term consumption remains poorly investigated. Our preliminary findings show that regular, long-term kratom use was not associated with altered biochemical parameters in a small sample of non-drug using kratom users. This suggests that long-term (>20 years) kratom use may not adversely affect the studied parameters. Our findings are in line with an earlier study indicating that kratom use was not harmful (13). However, more data and clinical investigations of kratom use are needed to establish its therapeutic value and safety.

In comparison to other haematological parameters, only the red cell distribution (RDW) value was found to be raised above the reference range. RDW is commonly used as a marker for detecting iron deficiency anaemia, as well as a predictor for inflammatory diseases such as chronic heart failure (18, 19). A previous study reported that elevation in RDW value was associated with increased risk of cardiovascular problems; however, other factors like poor nutritional intake and age-related diseases could have played a role in the elevation of RDW value (16, 19). Similarly, an increase in RDW value can also arise from defects in red cell production, or because of increased haemolysis (16). Though there were significant differences in the RBC, MCV and MCH values of those who consumed low (≤3 glasses) and higher (>3 glasses) quantities of kratom juice, all values of the parameters were within the normal reference range. Only the RDW value was slightly raised beyond the reference value for those who consumed a lower quantity of kratom juice (≤3 glasses) on a daily basis ($p<0.012$). The elevated RDW value can be a sign of cardiovascular risk or marker for inflammatory cytokines (16). However, the increase in the prevalence of anaemia with advancing age can also be partially attributed to the cytokines that inhibit the proliferation of erythroid progenitor cells (19).

In the West, users appeared prone to develop liver and kidney impairments even after using kratom for short durations (5, 7). This is in contrast to our findings that suggest that even long-term kratom consumption appears not to affect liver and kidney functions. Despite the non-significant differences in the cystatin C level between those who consumed either more or less quantity of kratom juice ($p<0.972$), we found cystatin C levels were slightly raised beyond the reference range. A previous study indicated that elevation of cystatin C level was linked with hypertension, coronary heart disease, rheumatoid arthritis and older age (20). Based on this, an inference of a possible link between long-term kratom use and increased cardiovascular risk might be made. Confirmation of this link, however, requires more controlled-clinical studies.

Besides the RDW and cystatin C levels, we found that long-term kratom users had elevated lipid profiles. The lipid profile (total cholesterol, LDL and triglycerides) of respondents were markedly raised beyond the reference range, regardless of the quantity of kratom consumed. The hs-CRP, homocysteine and apolipoproteins such as apolipoprotein B were higher among respondents who consumed more than 3 glasses of kratom daily. The elevation in total cholesterol, LDL, triglycerides, hs-CRP, homocysteine, apolipoprotein B and apolipoprotein B/APO A1 ratio may be indicative of elevated cardiovascular risk. Our findings were in line with an earlier study that also noted the elevation in LDL cholesterol with a higher intake of kratom juice (13). In another animal model study, the intake of kratom crude extracts of 100, 500 and 1000mg/kg was associated with a significant increase in triglycerides and cholesterol parameters in rats (21). Given its lipid-altering effects, long-term kratom use may potentially increase the cardiovascular risk among users.

In Asian societies people conceive opium consumption as having positive effects on cardiometabolic diseases (e.g. hypertension and dyslipidaemia) (22). It was reported that opiate use is associated with significant elevation in lipid profile (23). The mechanism behind this elevation remains poorly delineated, but the problem was shown to occur from both the decreased in hepatic clearance of LDL cholesterol from plasma, as well as the increase in hepatic synthesis of triglycerides (24). The findings from a review article indicated that opium (opioids) use is

linked with coronary artery disease (CAD) (22), although opium was reported to have both positive and negative cardiovascular effects (25). Opium addiction was found to have harmful effects on one or more lipid parameters leading to hypercholesterolemia (26).

Apolipoprotein A 1 and B, and hs-CRP (also known as a highly sensitive C-reactive protein/CRP) have been recognised as novel cardiovascular risk factors (28). Notably, we found kratom users in this study had elevated hs-CRP. The elevation of hs-CRP is reported to increase mortality risk (e.g. heart attack and stroke) (28, 29). The hs-CRP has opsonizing properties, where it can increase the risk of endothelial dysfunction (28). Perhaps, elevation in hs-CRP may indicate that kratom users could be at risk of developing atherosclerosis and myocardial infarction. This is because hs-CRP is reported to play an important role in several aspects of atherogenesis (e.g. release of proinflammatory cytokines, promotion of endothelial dysfunction, prevent nitric oxide production, etc.) (29). However, this alteration in hs-CRP parameter needs to be further investigated through proper clinical studies. Elevation in LDL and apolipoprotein B are associated with coronary heart disease (30). We found kratom users in this cohort had an altered LDL and apolipoprotein B. Indeed, the elevation in apolipoprotein B was associated with higher kratom intake (>3 glasses), and may serve as a risk factor for coronary heart disease. Our results also indicated that kratom users in this cohort had hyperhomocysteinemia. It has shown that the elevation in homocysteine levels can be related to various health conditions such as cardiovascular risk, neurological and psychiatric diseases (31). In fact, the prevalence of hyperhomocysteinemia is shown to be common among patients with heart diseases or high blood pressure (32). Despite the elevated cardiovascular risk, we found HDL cholesterol level was above the reference range among kratom users in this study, while apolipoprotein A was within the normal reference range.

We also found there were no alterations in the thyroid function and rheumatoid factor parameters of the respondents. It appears that regular kratom consumption in the form of a decoction did not impair their thyroid function. Since kratom use was associated with gastrointestinal discomfort like constipation, we also determined whether long-term kratom use can cause a severe gastrointestinal problem. CA 19.9 is usually used as a prognostic indicator in diagnosing gastric cancer (33). Respondents' CA 19.9 markers for gastric cancer were either negative or within the normal range. Thus, we found no link between regular kratom consumption and elevated risk of gastric cancer.

This study has a few limitations. First, our sample size was relatively small and consisted only of male respondents who were recruited through purposive sampling from one particular state without a control group. We decided not to recruit a control-group because the aim of the study was to determine the long-term (>20 years) effects of kratom use. We tried to recruit more long-term kratom users; however, most were excluded from the study since they had existing medical problems such as diabetes and hypertension, as well as previous illicit drug use history. Due to the small sample size, our findings cannot be generalised. Second, although all the respondents were long-term users (>20 years), some of the alterations in the haematological and biochemical parameters, specifically in the lipid profile (total cholesterol, LDL, triglycerides, hs-CRP and apolipoproteins B) could have been caused by other factors such as respondent's history of cigarette smoking, diet and lifestyle, and not kratom use per se. As such, it is vital that future studies attempt to determine the long-term effects of kratom use in regular users through a longitudinal clinical study. Finally, although the respondents self-reported the absence of pre-existing medical problems, we could not conclusively rule this out. This may have affected our findings.

CONCLUSION

Notwithstanding the vast evidence highlighting kratom's utility as a safe substitute to opioids, the popular notion that kratom is an opioid has compelled regulatory agencies to consider banning kratom use. In fact, though kratom consumption has been implicated in some deaths in the US, it has not been conclusively demonstrated that kratom was primarily or solely responsible for them (34). A recent study clearly pinpointed that 80% of kratom-related deaths occurred among those with history of substance misuse, and 90% had no evidence of a history of supervised pain care, suggesting strongly that the majority of the deaths were caused by the used of multiple drugs and not just kratom (35). Our findings are among the first to show in a cohort of non-drug using kratom users, that prolonged kratom use (>20 years with an average daily intake of ≥87.54mg of mitragynine), in the form of a brewed solution, was not associated with significant alterations in haematological and biochemical profile. However, there were indications that kratom use may increase cardiovascular risk, especially when used in large quantity for an extended period of time; this possible link necessitates further investigation.

ACKNOWLEDGEMENTS

This study was financially supported by the Ministry of Higher Education Malaysia under the Higher Institution Centres of Excellence (HICoE) grant.

REFERENCES

1. Singh D, Narayanan S, Vicknasingam B. Traditional and non-traditional uses of Mitragynine (Kratom): A survey of the literature. Brain Res. Bull. 2016; 126: 41-46.
2. Grundmann O. Patterns of Kratom use and health impact in the US-Results from an online survey.

Drug Alcohol Depend. 2017; 176: 63-70.
3. Kruegel AC, Grundmann O. The medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. Neuropharmacology. 2018; Vol. 134: 108-120.
4. Anwar M, Law R, Schier J. Notes from the Field: Kratom (Mitragyna speciosa) exposures reported to poison centers - United States, 2010-2015. MMWR Morbidity and Mortality Weekly Report. 2016: 65(29); 748-749.
5. Post S, Spiller HA, Chounthirath T, Smith GA. Kratom exposure reported to United States poison control centers: 2011-2017. Clin. Toxicol. 2019: Vol. 57(10); 847-854.
6. Lydecker AG, Sharma A, McCurdy CR, Avery BA, Babu KM, Boyer EW. Suspected Adulteration of Commercial Kratom Products with 7-Hydroxymitragynine. J. Med. Toxicol. 2016: 12(4); 341-349.
7. Corkery JM, Streete P, Claridge H. et al. Characteristics of deaths associated with kratom use. J Psychopharmacol. 2019: Vol. 33(9); 1102-1123.
8. Sabetghadam A, Ramanathan S, Sasidharan S, Mansor SM, 2013. Subchronic exposure to mitragynine, the principal alkaloid of Mitragynine speciosa, in rats. J Ethnopharmacol. 2013: 146; 815-823.
9. Matsunaga T, Morikawa Y, Kamase K, et al. Enhancement of Endothelial Barrier Permeability by Mitragynine. Biol. Pharm. Bull. 2017: 40; 1779-1783.
10. Lu J, Wei H, Wu, J. et al. Evaluation of the Cardiotoxicity of Mitragynine and Its Analogues Using Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes. PloS ONE. 2014: 9(12); e115648.
11. Tay YL, Teah YF, Chong YM. Mitragynine and its potential blocking effects on specific cardiac potassium channels. Toxicol. Appl. Pharmacol. 2016: 305; 22-39.
12. Manda VK, Avula B, Dale OR. et al. PXR mediated induction of CYP3A4, CYP1A2, and P-gp by Mitragyna speciosa and its alkaloids. Phytother Res. 2017: 31; 1935-1945.
13. Singh D, Muller CP, Murugaiyah V. et al. Evaluating the hematological and clinical-chemistry parameters of kratom (Mitragyna speciosa) users in Malaysia. J Ethnopharmacol. 2018a: 214; 197-206.
14. Sharma A, Kamble SH, Leon F. et al. Simultaneous quantification of ten key kratom alkaloids in Mitragyna speciosa leaf extracts and commercial products by ultra-performance liquid chromatography-tandem mass spectrometry. Drug Test Anal. 2019: Vol. 11, Issue 8.
15. Henningfield, JE., Grundmann, O., Babin, JK., Fant, RV., Wang, DW., Cone, EJ. Risk of death associated with kratom use compared to opioids. Prev Med. 2019: Vol. 128; 105851.
16. Felker GM, Allen LA, Pocock SJ. Red Cell Distribution Width as a Novel Prognostic Marker in Heart Failure. J Am Coll Cardiol. 2007: Vol. 50; 40-47.
17. Forhecz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohaszka Z, Janoskuti L. Red cell distribution width in heart failure: Prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. Am Heart J, Vol. 2009: 158(4); 659-666.
18. Cheng S, Han F, Wang Y. et al. The red distribution width and the platelet distribution width as prognostic predictors in gastric cancer. BMC Gastroenterology. 2017: 17: 163; 1-11.
19. Patel KV, Semba RD, Ferrucci L. Red Cell Distribution Width and Mortality in Older Adults: A Meta-analysis. J Gerontol A Biol Sci Med Sci. 2010: Vol. 65A (3); 258-265.
20. Wasen E, Isoaho R, Mattila K, Vahlberg T, Kivela SL, Irjala K. Serum Cystatin in the Aged: Relationship With Health Status. Am J Kidney Dis. 2003: Vol. 42; 36-43.
21. Harizal SN, Mansor SM, Hasnan J, Tharakan JKJ, Abdullah, J. Acute toxicity study of the standardized methanolic extract of Mitragyna speciosa Korth in Rodent. J Ethnopharmacol. 2010: 131; 404-409.
22. Masoudkabir F, Sarrafzadegan N, Eisenberg MJ. Effects of opium consumption on cardiometabolic diseases. Nat. Rev. Cardiol. 2013: 10; 733-740.
23. Bryant HU, Story JA, Yim GKW. Morphine-induced alterations in plasma and tissue cholesterol levels. Life Sci. 1987: Vol. 41(5); 545-554.
24. Mohammadi A, Darabi M, Nasry M. et al. Effect of opium addiction on lipid and atherosclerosis formation in hypercholesterolemic rabbits. Exp. Toxicol. Pathol. 2009: Vol. 61; 145-149.
25. Najafipour H, Beik A. The Impact of Opium Consumption on Blood Glucose, Serum Lipids and Blood Pressure, and Related Mechanisms. Front. Physiol. 2016: Vol. 7; 436, 1-12.
26. Aghadavoudi O, Eizadi-Mood N, Najarzadegan, MR. Comparing cardiovascular factors in opium abusers and non-users candidate for coronary artery bypass graft surgery. Adv Biomed Res. 2015: 4; 12.
27. Asgary S, Sarrafzadegan N, Naderi GA, Rozbehani R. Effects of opium addiction on new and traditional cardiovascular risk factors: do duration of addiction and route of administration matter? Lipids Health Dis. 2008: 7:42; 1-5.
28. Kamath DY, Xavier D, Sigamani A, Pais P. High sensitivity C-reactive protein (hsCRP) & cardiovascular disease: An Indian perspective. Indian J Med Res. 2015: 142; pp261-268.
29. Shrivastava AK, Singh HV, Raizada A, Singh SK. C-reactive protein, inflammation and coronary

heart disease. Egypt Heart J. 2015: 67; 89-97.
30. Contois JH, McConnell JP, Sethi AA. Et al. Apolipoprotein B and Cardiovascular Disease Risk: Position Statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. Clin Chem. 2009: 55:3; 407-419.
31. Chung, K. H., Chiou, H. Y., & Chen, Y. H. Association between serum homocysteine levels and anxiety and depression among children and adolescents in Taiwan. Scientific Reports. 2017: Vol. 7; 8330.
32. Asfar S, Safar HA. Homocysteine levels and peripheral arterial occlusive disease: a prospective cohort study and review of the literature. J Cardiovasc Surg. 2007: Vol. 48; 601-605.
33. Jo JC, Ryu MH, Koo DH. Et al. Serum CA 19.9 as a prognostic factor in patients with metastatic gastric cancer. Asia Pac J Clin Oncol. 2013: Vol. 9; 324-330.
34. Henningfield, JE., Fant RV., Wang, DW. The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. Psychopharmacology (Berl.). 2018: Vol. 235(2): 573-589.
35. Kuehn B. Kratom-Related Deaths. JAMA. 2019: Vol. 321; No. 20.