



Kratom (*Mitragyna speciosa*) dependence, withdrawal symptoms and craving in regular users



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ABSTRACT

Background: Kratom (*Mitragyna speciosa*) preparations have been traditionally used in Southeast Asia for its medicinal properties. Lately, Kratom use has spread to Europe and the US, where abuse potential and health hazards increasingly emerge. This study is the first to measure systematically Kratom dependence, withdrawal symptoms, and drug craving in regular Kratom users in Malaysia.

Methods: A cross-sectional survey of 293 regular Kratom users was conducted in the community across three northern peninsular states of Malaysia. The Leeds Dependence Questionnaire, Marijuana Withdrawal Checklist, and Marijuana Craving Questionnaire-Short Form were used to measure Kratom dependence, withdrawal and craving.

Results: More than half of the regular users (>6 month of use) developed severe Kratom dependence problems, while 45% showed a moderate Kratom dependence. Physical withdrawal symptoms commonly experienced include muscle spasms and pain, sleeping difficulty, watery eyes/nose, hot flashes, fever, decreased appetite, and diarrhoea. Psychological withdrawal symptoms commonly reported were restlessness, tension, anger, sadness, and nervousness. The average amount of the psychoactive compound, mitragynine, in a single dose of a Kratom drink was 79 mg, suggesting an average daily intake of 276.5 mg. Regular users who consumed ≥ 3 glasses Kratom per day, had higher odds of developing severe Kratom dependence, withdrawal symptoms, and inability to control Kratom craving.

Conclusions: The findings from this study show that regular Kratom use is associated with drug dependency, development of withdrawal symptoms, and craving. These symptoms become more severe with prolonged use and suggest a stronger control of the drug.

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1. Introduction

Kratom, also known as Ketum or 'biak', is an indigenous plant (*Mitragyna speciosa* Korth) of Southeast Asia. Kratom has gained widespread popularity as a folk remedy among the rural population of Malaysia and Thailand (Adkins et al., 2011; Hassan et al., 2013). People use Kratom leaves for their energising and pain relieving effects which are reported to have psychostimulant-as well as opiate-like character, depending on the dose consumed (Babu et al., 2008; Vicknasingam et al., 2010). The plant preparation is also used for opiate withdrawal and as substitution for the

more expensive heroin (Suwanlert, 1975; Assanangkornchai et al., 2007a,b; Vicknasingam et al., 2010; Ahmad and Aziz, 2012).

The main psychoactive alkaloid of Kratom is mitragynine while the strongest pain relieve is induced by the less abundant 7-hydroxy-mitragynine (Matsumoto et al., 2005; Hassan et al., 2013). Herbal preparations of Kratom are increasingly found and used in Europe and the US, either as pure preparation (Cornara et al., 2013; Forrester, 2013) or as one herbal ingredient of 'legal-' or 'herbal high' preparations, which are distributed under various names such as *Krypton*, *K2*, or *Spice* (Dresen et al., 2010; Arndt et al., 2011). While the main psychoactive components of these preparations are believed to be synthetic cannabinoids and herbs only being used as carriers (Cornara et al., 2013), a recent report identified a series of *K2* products that did not contain any known cannabinoid, but did contain mitragynine as psychoactive compound (Logan et al., 2012). Also purified mitragynine becomes increasingly available on a worldwide scale via the Internet (Boyer et al., 2008; Hillebrand et al., 2010; Schmidt et al., 2011). Emerging reports of Kratom

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use in the US and Europe suggest a considerable abuse potential with adverse health effects (Boyer et al., 2007, 2008; Havemann-Reinecke, 2011; Ward et al., 2011). Single case reports from Europe and the US are currently accumulating (Boyer et al., 2007, 2008; McWhirter and Morris, 2010; Havemann-Reinecke, 2011; Sheleg and Collins, 2011) which suggest an abuse and addiction potential, toxicity, and fatal interactions with other psychoactive drugs (Kapp et al., 2011; Neerman et al., 2013). A considerable addiction potential is now also supported by systematic animal studies (Yusoff et al., submitted for publication).

Kratom preparations are widely available on the Internet (Hillebrand et al., 2010; Schmidt et al., 2011). They are offered as resin, dried leaf, or powder under the names 'Kratom', 'Mitragyna', 'Concentrated Kratom', 'Plant sample Kratom', and many more. However, qualities vary considerably (Hanna, 2012). The long history of Kratom use in Southeast Asia allows western users via the Internet to access balanced and occasionally scientifically confirmed information on safety issues, dose patterns, potential side effects, and addiction potential of the drug (Siebert, 2012). In Malaysia, Thailand, and many EU countries, mitragynine and Kratom preparations are controlled drugs. In the US, UK, and Germany, they are currently not controlled substances but under surveillance awaiting more scientific evidence (EMCDDA, 2012; DEA, 2013; Hassan et al., 2013). Here we present the first systematic study of Kratom dependence, withdrawal symptoms, and craving in a human population of regular Kratom users in Malaysia.

2. Method

2.1. Study design

A cross-sectional study was conducted between January and December 2012 in three northern states (Penang, Perlis, and Kedah) of the peninsular Malaysia which neighbour the border of south Thailand. These are the states where Kratom is most prevalent in Malaysia. A total of 293 male Kratom users from various community settings were recruited through purposive sampling. Staff from the National Anti-Drug Agency and village heads helped introducing key informants who were familiar with the Kratom users in the respective communities. Key informants were briefed on the objective of the study and also trained how to approach Kratom users in the community. The tests were carried out in community settings including coffee-shops, community halls, clandestine Kratom makeshifts, and respondent's house using structured questionnaires which were translated into the local Malay language. Each interview session lasted between 30 and 45 min. Respondent were compensated with RM 20 (approx. USD 6) for their willingness to participate in the survey.

Urine toxicology tests for methamphetamine, amphetamine, opiates, cannabis, methadone, benzodiazepine, buprenorphine, and ketamine were conducted to exclude respondents who were tested positive for these drugs. This was to ensure that the reported behavioural effects were based on Kratom use only, and not due to the effects of other drugs. Importantly, respondents who used Kratom for less than six months were excluded from the study as they did not yet represent a regular use. The study was approved by the Human Ethics Committee of the Universiti Sains Malaysia.

2.2. Tests and data analysis

At present, there is no tool specifically designed to measure Kratom dependence, withdrawal symptoms, and craving in humans. Thus the Leeds Dependence Questionnaire (LDQ; Raistrick et al., 1994), Marijuana Withdrawal Checklist (MWC; Budney et al., 1999), and Marijuana Craving Questionnaire-Short Form (MCQ-SF; Heishman et al., 2009) were used in this study. We furthermore determined whether duration of use has an effect on severity of dependence, withdrawal, and craving in regular Kratom users. Respondents who had less than three years history of Kratom use were grouped as *medium-term user*, while those with more than three years history were grouped as *long-term user* and responses were compared between both groups.

2.3. Mitragynine analysis

In order to assess the amount of the psychoactive active compound in the local preparations, we measured mitragynine content in three Kratom juice samples as they are typically consumed. One fresh Kratom juice preparation (350 ml) was obtained at each of the three test sites. Chromatographic analysis was performed on an Agilent 1100 liquid chromatography system equipped with manual injector, quaternary HPLC pump, UV detector and ChemStation software for data collection

and analysis. The separation was performed on a Gemini-NX 5u C18 reversed phase column (Phenomenex, 10 mm × 4.6 mm) with a 20 µl injection volume. The mobile phased consisted of ammonium acetate, pH 5 (A) and acetonitrile (B). The flow rate was 1 ml/min with isocratic flow of A:B 65:35.

2.4. Statistical analysis

Respondents in this study were divided into two groups based on their Kratom use history. Those who had a less than three year history of Kratom use were grouped as *medium-term user* while those with a more than three year history of Kratom use were grouped as *long-term user*. The respective odds ratios (OR) and 95% confidence intervals (CI) were analysed for both groups. Chi-square tests were used to analyse the differences in Kratom dependence, withdrawal, and craving severity between medium- and long-term Kratom users. All statistical analyses were performed using SPSS 20 and VassarStats (<http://vassarstats.net/>). A significance level of $p < 0.05$ was used.

3. Results

3.1. Sociodemographic characteristics of Kratom users

Respondents in this study were all male Kratom users ($n = 293$), with the majority of Malay ethnicity. Respondents mean age in this study was 28.9 years. Nearly half were 18–25 years old. Less than 58% (171/293) were single. Two thirds have completed upper-secondary education (193/293) and more than two thirds held an employment (248/293). The majority worked as fisherman, farmers, drivers, and manual labourers. More than half earned between RM 100 and 1000 a month (the average monthly income in Malaysia is RM 5000; The Star, 31 March 2013). About 36% of the respondents were ex-drug users (107/293). More than half of the respondents (155/293) had 1–3 years history of Kratom use. Only 10% (28/293) had a ≥ 10 year history of Kratom use. Respondents mean age of first Kratom use in this study was 24.7 years. Almost half of them started using Kratom between the ages of 11–21 years. The average frequency of current Kratom consumption in the respondents was 3.5 times per day with a quantity of one glass Kratom juice per consumption episode. Each glass contains approx. 350 ml of fresh Kratom juice. About 13% (39/293) consumed 0.5–1.5 glasses of Kratom per day, 42% (124/293) consumed 2–3 glasses per day, and 44% (130/293) more than 3 glasses. Long-term user differed significantly from medium-term users in virtually all sociodemographic parameters (Table 1).

3.2. Kratom preparation and use

The leaves of the Kratom plant were used to prepare Kratom juice. One commonly reported way is to boil the leaves together with clean tap-water for approx. 3–4 h, until the mixture begins to emit a 'strong smell'. Consumers prefer to drink fresh Kratom juice which can be either served warm or chilled. Kratom juice is usually sold in packed plastic bags each containing about 250–350 ml. Although it is an offence to sell Kratom in Malaysia, it is sold furtively in few selected food-stalls frequented predominantly by manual labourers. Kratom is directly consumed from the purchased pack. It is commonly poured into a glass and drunk slowly during leisure time. Beginners prefer to mix sweet beverages (e.g., coke) with their Kratom drink in order to mask its bitter taste. Those who wish to obtain a better 'euphoria' or 'kick' usually mix cough-syrup (Dextromethorphan) or Erimin 5 (Nimetazepam) with the Kratom drink. The cost for processed Kratom juice varies and geographic factors influence the price. A pack Kratom (approx. 250 ml) was sold at the time of the testing for a price of RM 2.50–5.00. Regular Kratom users may consume a minimum of 3–4 packs per day. Usually, Kratom users do not know the purity level of their processed juice.

Table 1
Difference between medium- and long-term Kratom users ($n = 293$).

	<i>n</i> =	%	Medium-term user		Long-term user		<i>p</i> -Value
			<i>n</i> = 153	%	<i>n</i> = 140	%	
Marital status							
Married	118	40	52	34.0	66	47.1	0.022 *
Single/divorced	175	60	101	66.0	74	52.9	
Employment status							
Employed	248	85	122	79.7	126	90.0	0.015 *
Unemployed	45	15	31	20.3	14	10.0	
Accommodation							
Parents	142	48.5	92	60.1	50	35.7	0.001 *
Family/friends/others	151	51.5	61	39.9	90	64.3	
Income							
<1000	192	65.5	111	72.5	81	57.9	0.008 *
≥1001	101	34.5	42	27.5	59	42.1	
Age							
18–25 years	132	45	84	54.9	48	34.3	0.001 *
>26 years	161	55	69	45.1	92	65.7	
Ex-addict							
Yes	107	36.5	46	30.1	61	43.6	0.016 *
No	186	63.5	107	69.9	79	56.4	
Family use							
Yes	80	27	34	22.2	46	32.9	0.041 *
No	213	73	119	77.8	94	67.1	
Need to use ketum daily							
Yes	230	78.5	113	73.9	117	83.6	0.043 *
No	63	21.5	40	26.1	23	16.4	

* Note: Bold denote *p*-value (<0.05).

3.3. Reason for using Kratom

Respondents in this study reported to use Kratom for many different reasons. The majority used Kratom to enhance their physical energy. More than one third used Kratom because of curiosity and peer influence. About 15% (45/293) used Kratom to abstain from illicit drugs and alcohol, while about 13% (38/293) used Kratom to treat their medical problems (e.g., diabetes). Others used Kratom to improve their mood and overcome fatigue.

3.4. Kratom dependence

All regular users in this study claimed to be dependent on Kratom. More than half of the respondents (161/293) faced severe Kratom dependence problems, while 45% (132/293) had moderate Kratom dependence problems. More than 89% (262/293) of the regular users tried to abstain from Kratom in the past. About 90% (265/293) claimed that they have better social functioning when using Kratom. This was mainly because they were able to work long hours and to better socialise with their family members and friends. Almost 79% (230/293) reported that they needed to use Kratom daily. About 32% (95/293) of the respondents had increased their Kratom intake, while 42% (124/293) maintained their intake at rather constant level since the onset of their Kratom use.

Those who used more than 3 glasses of Kratom daily were more likely to report severe Kratom dependence than those who consumed less than 3 glasses (OR: 7.05; 95% CI: 4.09–12.13; $p < 0.001$). Similarly, those who used Kratom ≥3 times daily, were 5.19 times more likely to report severe Kratom dependence (OR: 5.19; 95% CI: 3.02–8.92; $p > 0.001$).

3.5. Kratom withdrawal – physiological symptoms

Physiological withdrawal symptoms encountered by Kratom users during withdrawal include sleeping difficulty, decreased appetite, nausea, vomiting, muscle spasm, sweating, fever, abdominal pain, diarrhoea, headaches, hot flashes, watery eyes and nose, hiccups, and shakiness or tremors. About 76% (222/293) of the Kratom users experienced body aches, including severe muscle

pain and cramps, after abstaining abruptly from Kratom use. About 65% (190/293) experienced mild withdrawal effects while 35% (103/293) experienced moderate to severe withdrawal effects after Kratom cessation. Kratom withdrawal symptoms were experienced for 1–3 days in 64% (187/293) of the regular users. In 36% (106/293) they lasted for more than 3 days.

Those who consumed ≥3 glasses of Kratom daily were more likely to report severe withdrawal symptoms during Kratom cessation (OR: 4.63; 95% CI: 2.46–8.71; $p < 0.001$), compared to those who drank less than 3 glasses of Kratom daily.

3.6. Kratom withdrawal – psychological symptoms

Psychological withdrawal symptoms commonly reported by the respondents in this study include nervousness, sadness, restlessness, anger, tension, and depressed mood. About 73% (151/293) of the respondents encountered at least five different psychological withdrawal symptoms during the first day of Kratom cessation. None of the respondents had any suicidal ideation after using Kratom for prolonged periods.

3.7. Kratom craving

About 23% (68/293) of the regular users reported high craving for Kratom while 77% admitted low craving. Those who consumed ≥3 glasses of Kratom daily were more likely to report higher craving for Kratom than those who consumed less than 3 glasses (OR: 4.8; CI: 2.09–11.10; $p < 0.001$). Only 2% (6/293) of the respondents have sought treatment for their Kratom use problems.

3.8. Medium-term vs. long-term Kratom use

There were no statistically significant differences in the reasons for Kratom use between medium- and long-term users ($p > 0.05$; Table 2). There were also no significant differences in Kratom dependence severity, withdrawal severity, and craving between medium-term and long-term Kratom users in this study ($p > 0.05$).

Table 2
Reasons for using Kratom.

	n=	%	Medium-term user		Long-term user	
			n = 153	%	n = 140	%
To enhance physical energy	83	28	44	28.8	39	27.9
Curiosity	61	21	35	22.9	26	18.6
Peer influence	46	16	30	19.6	16	11.4
To abstain from illicit drugs/alcohol	45	15	15	9.8	30	21.4
Self-treatment	38	13	22	14	16	11.4
To improve mood/ease boredom	17	6	6	3.9	11	7.9
To relieve fatigue	3	1	1	1	2	1.4

3.9. Mitragynine analysis

A consumption episode usually comprises the ingestion of one glass of Kratom juice (approx. 350 ml). Results from the analysis revealed a mitragynine content in the 350 ml Kratom juice sample acquired from Perlis of 83.4 mg, from Penang of 78.9 mg, and from Kedah of 74.6 mg (mean: 79.0 mg). On average, respondents in this study used 3.5 glasses of Kratom daily in each region. This means respondents ingested daily an average amount of 261.1–291.9 mg (mean: 276.5 mg) of mitragynine.

4. Discussion

Kratom is a widely used psychoactive drug in Southeast Asia which is currently spreading to other parts of the world (e.g., Forrester, 2013). Although anecdotal reports are available (Suwanlert, 1975), this study is the first to measure systematically Kratom dependence, withdrawal symptoms, and craving in regular Kratom users in the northern states of the peninsular Malaysia. All the respondents in this study were dependent on Kratom and also encountered unpleasant withdrawal symptoms and craving after trying to abstain from Kratom use.

Kratom is viewed as a cheap psychotropic drug with dual-properties. It can be used as a stimulant drug to enhance physical tolerance, or as an analgesic due to its pain-relieving properties. All respondents in this study were dependent on Kratom. They believed that Kratom is not as harmful as other available drugs, such as methamphetamine or heroin. Most users shared the belief that it is better to use Kratom in order to improve work performance than using illicit stimulant-drugs which would also be more expensive. Those who claimed that they use Kratom to enhance their work performances, actually use Kratom as an 'energy boosting drink'. Respondents claimed that Kratom induces stimulant like-effects when it is use in small quantity especially under the burning sun or when engaging in an exhausting work. Sedating effects, in turn, are reported when Kratom is used excessively or when slowly consumed at leisure time, e.g., at social gatherings with friends. The Malay village community does usually not discriminate Kratom users because they regard the Kratom using practice as an inherent aspect of their ancestral tradition. They see the Kratom using habit as an integral part of their present culture, and, hence, Kratom users as 'diligent' and 'hard working', while e.g., cannabis users are 'lazy' (Saingam et al., 2013). This is in line with anecdotal reports were Kratom users became dependent to Kratom because they wanted to work more efficiently in their rice mills (Suwanlert, 1975). There was a very low rate of treatment seeking among the regular Kratom users in this study. They viewed their Kratom dependence as non-problematic and something which they could deal with by themselves. At this point it will be interesting to assess behavioural impairments that result from regular Kratom use and dependence. Systematic research on this question is warranted.

In Southeast Asia, Kratom use may represent another case of systematic drug instrumentalization on daily basis (Müller and

Schumann, 2011a). Psychoactive drugs can be instrumentalized for various purposes. Thereby, the drug-induced change in the mental state facilitates the more effective pursuit of another, originally drug-independent task. It was claimed that most of the non-addicted psychoactive drug use in the world is based on drug instrumentalization rather than on the direct pharmacological reinforcing effects of the drug (Müller and Schumann, 2011a). However, a successful instrumentalization may under certain circumstance pave the way to enhanced and prolonged drug use, which may eventually lead to drug addiction (Müller and Schumann, 2011b). From the reports of Kratom use in order to enhance work output and to recover from exhausting work, one may speculate that the easy availability of this 'drug instrument' and the lack of alternative instruments in rural Malaysia may foster systematic Kratom use and the transition to Kratom dependence.

Findings from this study showed that more than half of the respondents had severe Kratom dependence problems. All others had moderate Kratom dependence problems. A sizable proportion of the respondents in this study could usually not endure the first day of Kratom withdrawal symptoms as the symptoms disrupt their physical and psychological functioning. Although the withdrawal symptoms lasted only for a short period of a few days and gradually subsided, the pain that they experienced severely affected their work performance and mental occupation. Most respondents tried to self-medicate their withdrawal symptoms with sleeping pills. The withdrawal symptoms in this study were similar to the symptoms reported in previous reports from Malaysia and Thailand (Suwanlert, 1975; Assanangkornchai et al., 2007a,b; Vicknasingam et al., 2010; Ahmad and Aziz, 2012; Saingam et al., 2013), but are less severe than those reported after excessive Kratom consumption in the US or Europe (McWhirter and Morris, 2010; Sheleg and Collins, 2011; Kapp et al., 2011). The reason for this discrepancy may be a better social control of the consumption in regions with historically established Kratom consumption and a somewhat better predictability of the Kratom quality. Also, the use of highly concentrated plant extracts as it was reported in Europe and the US may lead to a significant escalation and stronger withdrawal effects in Kratom consumers (Havemann-Reinecke, 2011).

In this study, those who drank Kratom several times per day for more than 6 month were regarded as regular Kratom users. Thirty-six percent of the respondents had previous history of substance abuse problems. When probed, most respondents reported being previously dependent on cannabis, heroin, and methamphetamine. Respondents claimed that they use Kratom juice to treat and reduce their dependence on illicit drugs. In fact now they used Kratom as a substitute for the illicit drugs. None of the respondents were tested positive for using illicit drugs during the interview which may suggest a certain efficacy as a substitute drug. The use of Kratom and mitragynine as a substituting drug for heroin was also reported in the US, although with mixed success (Boyer et al., 2007, 2008; Neerman et al., 2013). To what extent Kratom may be used to substitute heroin and being used effectively for drug addiction treatment is an open question that awaits systematic research.

The average mitragynine content in each glass Kratom was 79.0 mg suggesting a total daily dose of 276.5 mg mitragynine in this study. This is more than previously estimated in Thailand and Malaysia (Suwanlert, 1975; Vicknasingam et al., 2010; Saingam et al., 2013). Amounts of mitragynine consumed by western Kratom abusers are currently unclear. On average, regular Kratom users in this study used Kratom 3.5 times per day. Most of them used Kratom in the morning, afternoon, and evening. Kratom users reported that they need to use Kratom in the morning to boost their energy levels and to motivate themselves to work. In the evenings, they normally used Kratom to combat fatigue and to help them to 'mingle and chat' with their colleagues in the village.

Craving for Kratom was reported by all regular users with most of them admitting a moderate level. High craving coincided with high Kratom consumption, but was not dependent on the length of the consumption. This is in line with case reports from western users, who showed a strong craving and subsequent escalation of consumption (Havemann-Reinecke, 2011). At present, there is no specific treatment for Kratom dependence. There have been cases where Kratom users try to use methadone and benzodiazepines to treat their Kratom dependence. The unsupervised use of methadone and benzodiazepines among Kratom users could impose an additional risk of overdose (Neerman et al., 2013). Many habitual Kratom users are unable to quit from Kratom use, because of its chronic withdrawal symptoms, e.g., sleeping problems and chronic pain during the first day of abrupt cessation.

This study is the first to systematically measure Kratom dependence, withdrawal, and craving in regular Kratom users. It clearly shows in a population of Malaysian consumers that regular Kratom use may lead to drug dependence with profound withdrawal symptoms and subsequent drug craving in circumstances where consumption is socially controlled. These findings may also suggest a closer monitoring of Kratom preparations and of 'legal high' preparations which contain Kratom in regions where the availability and consumption only recently emerged (Logan et al., 2012; Forrester, 2013). Findings from this study may help medical practitioners to better understand the effects of prolonged Kratom use in humans. Its efficacy as an adjunct for opiate addiction therapy, however, might need thorough investigation from a broader perspective.

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The funders had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

DS and BKV designed the study. DS, BKV, and CPM obtained the funding. DS performed the experiment. DS, BKV, and CPM analysed the data and wrote the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors reported no biomedical financial interests or potential conflicts of interest.

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