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Review

Traditional and non-traditional uses of Mitragynine (Kratom): A survey of the literature

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ABSTRACT

Introduction: The objective of the paper was to highlight the differences in the traditional and non-traditional users of kratom in the South East Asian and Western contexts.
Method: A literature survey of published kratom studies among humans was conducted. Forty published studies relevant to the objective were reviewed.
Results: Apart from the differences in the sources of supply, patterns of use and social acceptability of kratom within these two regions, the most interesting finding is its evolution to a recreational drug in both settings and the severity of the adverse effects of kratom use reported in the West. While several cases of toxicity and death have emerged in the West, such reports have been non-existent in South East Asia where kratom has had a longer history of use. We highlight the possible reasons for this as discussed in the literature. More importantly, it should be borne in mind that the individual clinical case-reports emerging from the West that link kratom use to adverse reactions or fatalities frequently pertained to kratom used together with other substances. Therefore, there is a danger of these reports being used to strengthen the case for legal sanction against kratom. This would be unfortunate since the experiences from South East Asia suggest considerable potential for therapeutic use among people who use drugs.
Conclusion: Despite its addictive properties, reported side-effects and its tendency to be used a recreational drug, more scientific clinical human studies are necessary to determine its potential therapeutic value.

Contents

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1. Introduction

Mitragyna speciosa is a tree that has been reportedly found in the Philippines islands, Borneo and New Guinea (Lee, 1957).[1] However, most published works in the past have focussed on its use in Thailand and Northern Malaya. More recently, reports of kratom use in the West have emerged.

Mitragyna speciosa Korth (*M. speciosa*) from the Rubiaceae family is a tropical plant and *mitragynine* and *7-hydroxymitragynine* are the active compounds of *M. speciosa*. Both these alkaloids produce dose-dependent narcotic effects, stimulant effects at lower doses and sedative-like effects at higher doses (Babu et al., 2008). There have been other studies that have reviewed the properties of kratom in detail (Jansen and Prast, 1988a; Hassan et al., 2013; Babu et al., 2008; Adkins et al., 2011; Rosenbaum et al., 2012; Prozialeck et al., 2012 and Cinosi et al., 2015). The tree has been known variously as Katawan, Kratawm, Tawn, in Thailand and as Ketum, Kutum, Bia or Biak in Malaysia (Burkill, 1935). In this paper we will use the widely used name, Kratom, derived from the Thai names for the tree.

This paper provides a broad survey of the well documented traditional uses of kratom and the less well known, non-traditional uses of kratom in Thailand and the northern states of peninsula Malaysia (collectively referred to as South East Asia for convenience) and the US and Europe (collectively termed Western countries). In doing so, we highlight the major differences in the use of kratom in these two different regional contexts.

2. Method

A literature review search was conducted through PubMed, Science Direct and Scopus to gather published articles on kratom use. Some of the keywords that were used to assist in the literature search include: *"Kratom"* and *"Mitragyna speciosa"*. Forty published articles describing kratom use in humans were found; seventeen articles on kratom use in Malaysia and Thailand and twenty three articles on kratom use in the West (USA; Germany; Sweden; Norway and UK). Interestingly; although there were repeated references in the literature to kratom being found in other parts of South East Asia such as the Philippines; Myanmar and the Borneo states; published studies of kratom use are confined to Thailand and Malaysia.

The types of studies were divided by their study design; surveys which included internet surveys (10); review papers (8); case reports (17); qualitative in-depth interviews (2); reference text (1); short communications (2); and experimental design (1).

3. Results

3.1. Modes of supply

In Thailand, regular users have their own trees hidden in their rubber plantations, rice fields, fruit garden, yards of homes, ditches or near fishing ponds. While fresh kratom could also be purchased from the market in the past, this mode is no longer available as the plant is illegal. This has been replaced by the kratom salesman who delivers the product to known users.

Secret purchases can also be made from those with trees, a tea shop or from other villages (Saingam et al., 2012).

Also in Malaysia some users were found to be cultivating their own trees; most however obtained their supply from familiar suppliers or local coffee shops where it is sold openly, despite the ban on kratom. Coffee shops sell a prepared solution which is ready for immediate consumption (Vicknasingam et al., 2010). The common element is that both in Thailand and Malaysia, the quality of the product is known as are the sources of supply and suppliers.

In contrast, purchases in the West are made without personal contact with the supplier or knowledge regarding the quality of the kratom product being supplied. In the US, powdered kratom leaves can be purchased from head shops, kava bars and via the internet. The largest volume of sales appears to be via the internet (Babu et al., 2008; Rosenbaum et al., 2012) probably because it ensures anonymity of the buyer. It is also sold in the form of tablets, capsules, gums, leaves for chewing or brewing and extracts for smoking (cited in Warner et al., 2016).

It is usually marketed as a dietary supplement (Boyer et al., 2007, 2008; Sheleg and Collins, 2011). The safety of many of the internet acquired kratom product has been compromised by insufficient information regarding the product, its side effects and warnings about possible toxicity. Many users are led to believe that kratom can be used as a safe herbal remedy (Schmidt et al., 2011; Rosenbaum et al., 2012).

3.2. Modes of consumption

In South East Asia, kratom leaves are smoked, chewed or brewed and ingested as an herbal solution. The chewing of kratom leaves is common among the Thais, while in Malaysia it is commonly consumed as a juice. Habitual users usually consume kratom juice at least 3 times a day in varying quantities (Suwanlert, 1975; Ahmad and Aziz, 2012). Kratom has a bitter taste and therefore some individuals prefer to mix their kratom drinks with sweet beverages (e.g. Coca-Cola, Pepsi, etc.). There have also been occasions where kratom users spike their drinks with other potentially harmful substances such as cough syrup and sleeping pills (Tungtananuwat and Lawanprasert, 2010).

Modes of consumption in the West are less clear but can be inferred from the nature of preparations available for sale. These include leaves for chewing and brewing, powders, gums, capsules, pills and extracts for smokers (cited in Warner et al., 2016).

3.3. Uses of kratom

In South East Asia, kratom leaves have been traditionally used for its medicinal value in treating mild medical problems such as fever, diarrhoea, diabetes, pain and as a wound poultice (Hassan et al., 2013). Kratom use is widespread among rural-folk in the Northern Peninsular states of Malaysia and Southern Thailand (Burkill, 1935; Suwanlert,1975; Cinosi et al., 2015). Apart from its healing properties, male manual labourers (such as farmers, rubber-tappers, fisherman, and machine operators) commonly use kratom leaves for its coca and opium-like effects to enhance physical endurance and as a means to overcome stress (Suwanlert, 1975; Assanangkornchai et al., 2007a; Saingam et al., 2012; Vicknasingam et al., 2010; Ahmad and Aziz, 2012). Some also reported that it heightened sex desire (Vicknasingam et al., 2010).

Females normally use kratom for its curative properties in the treatment of mild cases of fever, diarrhoea and pain. In fact, while male users face no censure or stigma in society, female kratom addicts are not accepted (Suwanlert, 1975; Assanangkornchai et al., 2007a). There is also an early record of kratom being used in Malaya as an affordable opium substitute (Burkill, 1935). Tanguay (2011) cites a claim that kratom was also being used to ease opiate withdrawal in Thailand, as early as in the 1940s. However, subsequent Thai studies have not reported any evidence of this practice (Suwanlert, 1975; Assanangkornchai et al., 2007a). The first report of the common use of kratom as a cheap substitute for reducing dependence on other illicit substances like cannabis, morphine and

[1] Mistakenly cited as Thuan (1957) in almost all papers.

amphetamine-type-stimulants and also to suppress opiate withdrawal symptoms was presented by Vicknasingam et al. (2010). They found that users in the northern Malaysian states were relying on kratom for these purposes because it was cheap, and easily available and, in the case of those facing opiate withdrawal symptoms, obviated the need to approach government facilities that might expose their identities.

Tanguay (2011) reports a more recent drug use trend among the young (teenagers to individuals in their 30s) in Thailand who boil kratom leaves as a base for a cocktail named, '4 × 100'. It is made up of kratom tea, cough syrup, Coca-Cola and ice cubes. Consumption of this concoction is, however, less accepted by the general community. Fears of censure from the community and arrests by law enforcement agencies have therefore pushed the use of such concoctions to 'hidden settings'.

In the West, kratom has been traditionally used to manage pain due to its analgesic properties. It is often marketed as a safe herbal dietary supplement to treat chronic pain. It quickly became viewed as an economical alternative to self-treat pain from prescription opioid withdrawal as well (Boyer et al., 2007, 2008; McWhirther and Morris, 2010; Nelsen et al., 2010; Neerman et al., 2013; McIntyre et al., 2015). There was also one reported case of using kratom to self-manage alcohol withdrawal symptoms from Germany. It was estimated that a daily dose of 15 g of kratom was equivalent to about 45 mg of morphine (Havemann-Reinecke, 2011).

More recently, kratom has gained popularity for its euphoric effects and is being popularized as a safe herbal product capable of giving a 'legal' high (Swogger et al., 2015), and as an alternative to other sedative and stimulant type drugs (Warner et al., 2016). Combinations of kratom with other substances are also being sold via the internet promising a more powerful high. One such concoction is 'krypton' which combines powdered kartom leaves with *O*-Desmethyltramadol. Kronstrand et al. (2011) present nine cases of death in less than a year linked to the overdose of this combination in Sweden.

It has therefore clear that kratom is rapidly morphing into a recreational drug not only in the West but also in Thailand where it is gaining popularity among younger individuals and even high school students (Assanangkornchai et al., 2007b).

3.4. Reported side-effects of kratom

The main side effects reported after more than a year of regular consumption are loss of weight, dehydration (resulting in increased thirst), constipation and hyper pigmentation. Longer period users also report lethargy and tiredness (Vicknasingam et al., 2010; Saingam et al., 2012). The property of kratom to act both as a stimulant and a sedative is dose dependent. The former effect is felt at lower doses while the latter is experienced at higher doses (Babu et al., 2008). However, regular users are prone to develop tolerance and often increase their intake over time (Suwanlert, 1975) and kratom is addictive (Suwanlert, 1975; Ahmad and Aziz, 2012; Vicknasingam et al., 2010; Singh et al., 2014).

Kratom users in Thailand have their own traditional ways of ameliorating side effects like constipation, fatigue, shaking of hands and headaches. The methods include chewing the leaves without swallowing, drinking plenty of water and increasing the intake of sour fruits and vegetables (Assanangkornchai et al., 2007a). Others worked even harder, consumed cold water, took cold showers or simply slept (Saingam et al., 2012).

The side effects of kratom in the Western context must be deduced from case reports since no large face-to-face surveys of users have been conducted. Kapp et al. (2011) report the case of an individual who started with ingesting one (2.3–3.5 g) or two tablespoons of powdered kratom and had reached four to six teaspoons daily over the course of two weeks. He was taking no other supplements or alcohol. He found that it was mildly relaxing, but induced tiredness and a loss of appetite. Two cases of kratom use linked with seizures were reported (Boyer et al., 2008; Roche et al., 2009) though these links could not be firmly established. Nelsen et al. (2010), however, provide firmer evidence of seizure and coma after ingestion of kratom. Sheleg and Collins (2011) present a case of hypothyroidism in a kratom using male and discuss the possibility that the major alkaloid identified from kratom might interfere with the functioning of the thyroid gland. The patient also gained 60 pounds, became lethargic and developed myxedematous face, the extreme manifestation of hypothyroidism.

Forrester (2013) discusses 14 cases, comprising of eight who only abused kratom while the rest were using other substances as well. He noted that the positive effects from ingesting kratom was similar to those reported previously (in South East Asian studies).

A qualitative analysis of the experiences of kratom uses filed in the internet site Erowid.org offers more insights on the effects of kratom use (Swogger et al., 2015). Based on 161 reports that included 109 males, 13 females and the rest who did not identify their gender, the following summary of positive and negative effects emerge. On the positive side, many users reported at least some of the following effects: euphoria, a sense of wellbeing, relaxation, enhanced sociability, more energy, analgesia, sensory enhancement, and a warm and tingly feeling. On the negative side, reports of nausea, stomach aches, alternating between chills and sweats, dizziness, vomiting, itching, numbness in the mouth and throat, sedation, visual alterations and unsteadiness were filed.

While some effects parallel those reported in the South East Asian context, others do not. For example, reports of constipation, and hyper pigmentation are absent. By the same token reports of seizures and coma were absent in the South East Asian context. Furthermore, reports of kratom toxicity and mortality continue to emerge in the West (Nelsen et al., 2010; McWhirther and Morris, 2010; Kronstrand et al., 2011; Holler et al., 2011; Sheleg and Collins, 2011; Forrester, 2013; Neerman et al., 2013; Karinen et al., 2010; Dorman et al., 2014; McIntyre et al., 2015), while none have been reported in South East Asian. Many, though not all, cases of fatality, involved individuals who had abused other substances along with kratom or had histories of alcohol dependence (McIntyre et al., 2015) or heroin abuse (Neerman et al., 2013).

Injury to the liver has also been linked to kratom ingestion. A report from Germany described the case of a 25-year-old man who developed intrahepatic cholestasis (impaired flow of bile inside the liver) after consuming high doses of kratom powder for two weeks. A liver biopsy confirmed the drug-induced cholestatic injury after other potential causes were ruled out. Furthermore, alkaloids consistent with kratom ingestion were detected in the urine. Although the powder was purchased via the internet, analysis revealed no adulterants or contaminants (Kapp et al., 2011). A similar case of a Caucasian man aged 58 suffering from cholestatic hepatitis was linked to prolonged use of kratom. He had taken kratom to relieve anxiety and to relax; his problem was resolved when he went off kratom and recurred with the resumption of consumption of the same kratom preparation. Other causes for the liver condition were ruled out. The authors observe that despite the long history of kratom use in South East Asia, reports of liver injury were non-existent, unlike in the Western context. They posit that liver injury may be due to the presence of 'a contaminant or error in identification or preparation of the herbal product'.

There have been no reports of toxicity or death due to kratom use in South East Asia. This either suggests that users tolerate kratom well due to its long history of use or simply because cases of toxicity or adverse reactions go unreported. Since kratom use is widespread in rural settings it is unlikely that formal medical assistance will be sought in the event of adverse reactions. Jansen and Prast (1988a,b),

on the other hand, speculate that the pharmacological profile of pure mitragynine consumed in the West and the unprocessed leaf used in South East Asia may also explain the difference since the latter may contain other substances that modify the effects of the drug.

In any event, only one study in Thailand has documented cases of kratom poisoning and adverse withdrawal symptoms among users. Most of the respondents who reported kratom poisoning and withdrawal symptoms were found to be under the influence of other illicit drugs such as codeine (Trakulsrichai et al., 2013). There have also been anecdotal reports pertaining to concoctions of kratom with codeine or cough syrup (Tungtananuwat and Lawanprasert, 2010; Singh et al., 2014).

3.5. Addiction

Regular or long term use of kratom develops dependence; addiction has been reported in several early studies (Lee, 1957; Assanangkornchai et al., 2007a; Saingam et al., 2012). Results from a more recent Malaysian study indicated that more than half (55%) of the regular kratom users developed severe dependence.

Reports of dependence on kratom in the West emerge from case reports from the UK (Boyer et al., 2008; McWhirter and Morris, 2010), Germany (Kapp et al., 2011) and the US (Dorman et al., 2014; Nelsen et al., 2010; Forrester, 2013; Sheleg and Collins, 2011). It can be surmised that given the large and growing number of internet purchase sites for kratom (cited in Cinosi et al., 2015), addiction to kratom is also likely be growing in the Western country context.

3.6. Withdrawal effects

Abrupt cessation can cause a variety of unpleasant physical and psychological symptoms. The physical symptoms include lethargy irritability, frequent yawning, runny nose, muscular pain, cramps joint pain and diarrhoea (Suwanlert, 1975; Saingam et al., 2013, 2014, 2016). The psychological symptoms include restlessness, tension, aggression, sadness, nervousness, delusion, hallucination, and intense craving. Feelings of anxiety, depression, moodiness, annoyance and sleeplessness were also reported (Lee, 1957; Suwanlert, 1975; Assanangkornchai et al., 2007a; Vicknasingam et al., 2010; Saingam et al., 2013; Ahmad and Aziz, 2012; Singh et al., 2014). In many cases, long-term users had difficulty in giving up regular kratom use (Suwanlert, 1975; Singh et al., 2014). Tanguay (2011) reports that while kratom withdrawal symptoms are annoying and distracting, they were not as painful as in the case of opiate withdrawal symptoms. A survey of users in Malaysia found that respondents who consumed $\geq$3 glasses of kratom juice daily (approximately of 276.5 mg of mitragynine) had higher odds of developing severe kratom dependence and withdrawal symptoms. It was also noted that the withdrawal symptoms usually disappear after 1–3 days (Singh et al., 2014).

Despite kratom dependence, many users remain in good health and functioned normally. A case report by Lee (1957) discussed the case of a chronic kratom user, who had marked withdrawal symptoms during cessation, but was observed to otherwise be in good health; he had suffered no weight loss and was mentally and physically normal. More recently, a Malaysian study found no significant impairment in the social-functioning of kratom users. Furthermore, none of the respondents were involved in risky drug using or criminal behaviours (Singh et al., 2015).

Withdrawal symptoms in the West have been documented formally less extensively, in the absence of large surveys of kratom users. The kratom user is identified only when he or she seeks treatment for dependence or other complications arising from its use. Again, based on case reports some withdrawal effects can be identified.

In the case reported by Kapp et al. (2011) insomnia and restlessness followed the cessation of use, although the authors caution that severe itching of the skin (pruritus) experienced by the individual could have contributed to these symptoms. A male with alcohol dependence in the UK complained of anxiety, restlessness, tremor, sweating, craving, itch, and feelings of dread. However, the symptoms were described as being 'short and benign' (McWhirter and Morris, 2010). A male from Germany admitted for intrahepatic cholestatis described his withdrawal symptoms as follows: fever and chills that lasted a week followed by mild abdominal pain that developed into severe abdominal pain. This was accompanied by a brown coloration of the urine (Kapp et al., 2011). But these symptoms could well be associated with the liver complication he developed. A patient in the US who presented with the coincidence of addiction to kratom and developed hypothyroidism complained of opiate-type withdrawal symptoms (cramping, abdominal pain, sweating and diarrhoea) which resolved three days after treatment (Sheleg and Collins, 2011)

Boyer et al. (2008), presented a male subject who took kratom to overcome withdrawal from hydromorphine. He had combined it with modafinil and reportedly experienced tonic-clonic seizures (a type of generalized seizure affecting the entire brain). Withdrawal symptoms included runny nose, insomnia, poor concentration, constricted affect and muscular pains. Withdrawal from kratom was noted to be less intense but more protracted than from prescription opioids.

3.7. Legal status

Kratom is still viewed as an addictive psychotropic plant since its effects resemble those of other psychotropic substances (Tanguay, 2011). Kratom is currently banned and controlled under the Poisons Act 1953 in Malaysia. Those found guilty of distributing kratom leaves or preparations illegally can be fined up to RM10,000 (approximately USD = 2500), or be sentenced to jail for up to 4 years (Vicknasingam et al., 2010). The cultivation of kratom is, however, not an offence in Malaysia. Despite legal sanctions, processed kratom juice can be acquired with ease from illegal kratom traders in the community (Vicknasingam et al., 2010).

In Thailand, kratom was first regulated under the Kratom Act 1943 but has been reclassified in 1979 under the Narcotic Act. The planting, possession, import and export of kratom leaves are now considered illegal (Assanangkornchai et al., 2007a).

In the West kratom is known as a safe *legal-high* (Schmidt et al., 2011; Cinosi et al., 2015). Though the Food and Drug Administration (FDA) of US has released an import alert cautioning the side-effects of kratom use in humans, kratom is still not regulated in the US and UK. Kratom is currently controlled in several EU member states such as Denmark, Finland, Lithuania, Poland, Romania and Sweden (EMCDDA) (cited in Forrester, 2013). Kratom is banned in Australia, Bhutan, Malaysia, Myanmar (Burma), and Thailand. Some of these countries impose severe penalties for possession of Kratom. It is legal in most other countries while a 2012 review reports that Kratom is still legal in the United States, although the US Drug Enforcement Administration has placed Kratom on its list of "Drugs and Chemicals of Concern." (Prozialeck et al., 2012). It is a controlled substance in Indiana, Tennessee, Vermont, and Wisconsin but they have banned possession of the primary active chemical constituents of kratom.

It is challenging to detect kratom users in the community and equally difficult to screen them for the presence of mitragynine. There are no urine-test-kits for detecting mitragynine presence in human. Most of the kratom screening processes are carried out using more advanced systems (Rosenbaum et al., 2012; Kowalczuk et al., 2013). This undermines the efforts of drug enforcement authorities and healthcare providers to detect kratom users and

provide them treatment. Another hurdle is the fact that there is also no standard or proper treatment protocols developed for kratom dependence

3.8. Social status

In South East Asia, while users may face rebuke from family for engaging in the 'wasteful' kratom use habit (Ahmad and Aziz, 2012), they are neither discriminated against, nor are they stereotyped as drug users (Saingam et al., 2013). They are usually seen as hardworking individuals who used kratom to enable them to work longer hours and earn extra income (Suwanlert, 1975). The majority of regular kratom users are older individuals, with regular employment, and are married and living with their family (Suwanlert, 1975; Assanangkornchai et al., 2007a; Vicknasingam et al., 2010). Another aspect, recently highlighted by Saingam et al. (2016) is that kratom had an important role in traditional Thai culture as it was used as a snack to receive guests and was part of the ritual worship of ancestors and gods.

4. Discussion and conclusions

Kratom has a long history of use in South East Asia though the earliest reference to it in the literature might well be the 1929 and 1934 reports of Marcan to the government of Siam that opined that kratom habit did not have the bad reputation associated with opium smoking (as quoted by Lee, 1957). While it is acknowledged in the literature that kratom use in the West has more recent origins we were unable to find any reference as to when exactly it received formal recognition.

Both in South East Asia and the West, kratom has moved away gradually from its traditional uses (to increase physical endurance and to treat several physical maladies) to newer uses with potential promise. Vicknasingam et al. (2010) reported that in parts of Northern peninsula Malaysia kratom was being used as a traditional alternative to manage drug withdrawal symptoms because it was affordable, easily available and apparently had no serious side effects despite prolonged use. More importantly, it enables self-treatment that avoids stigmatization as a drug dependent. These claims merit further serious scientific investigation since it holds out the possibility of kratom being developed as a low-cost alternative therapy, particularly in developing countries. In the West, kratom was valued for its analgesic effects but has more recently been used by individuals to aid in managing opioid withdrawal. While some of these individual attempts have resulted in cases of toxicity and fatalities, the value of kratom in pain management and opioid withdrawal deserves careful scientific study and evaluation to determine its efficacy, composition, drug interactions and safe dosage limits. In any event, any blanket illegalization of kratom poses the danger of casting out the baby with the bathwater. It is also interesting that evidence from both regions appear unanimous on one point; the withdrawal symptoms from kratom were less intense than that from prescription opioids or illicit substances.

The marked absence of cross-sectional studies recording the subjective experiences of users in the Western context provides a contrast to the many such studies in South East Asia. This is probably because kratom use in the West is largely an individual endeavour and does not enjoy the social acceptance that it does (or did) in the South East Asian context. Thus records of subjective experiences have to be pieced together from case reports or from experiences shared via internet forums. There is therefore a need for large, systematically designed studies to document the experiences of Western users.

There is also the emerging trend of relying on kratom as a cheaper and more easily available substitute recreational drug in both South East Asia and the West. It was reportedly gaining popularity as a recreational drug among the young, at least in Thailand. Kratom mixed with other substances have spawned variations such as the '4 × 100' promising to deliver a bigger 'high'. In the West too, it is gaining popularity as an herbal based product that delivers a 'safe high' with variations such as krypton in Sweden that has proved to be a powerful and sometimes fatal cocktail. While these developments are a cause for concern, they only underscore the need for regulation, not necessarily a ban on the use of kratom.

The severe side effects linked with kratom use reported in the West (liver disorders, cases of toxicity and fatalities) are virtually unknown in the South East Asia. One theory is that the powdered, refined form of kratom available in the West may have a different effect on humans as compared to the fresh leaves chewed or boiled in South East Asia (Jansen and Prast, 1988a,b). Besides, the constituents of kratom leaves itself are believed to have a wide variation of effects, depending on their strain and source. This suggests that further research might do better to focus on kratom leaves as a whole rather than just on isolated compounds such as mitragynine.

Another speculation is that the samples available in the West may have contaminants or suffer from errors in identification or preparation of the herbal product. A third possibility may be the differences in dosage generally used in both regions. Internet sales and the lack of personal contact between buyers and sellers may be a source of misinformation on the quality, use, dose and precautions regarding kratom use. This may be a contributory cause to the more frequently reported cases of toxicity and death in the West. In any case, this aspect is a rich area for research.

The lack of a convenient test-kit for detecting mitragynine presence in humans undermines the efforts of drug enforcement authorities and healthcare providers to detect kratom users and provide them support. The other hurdle is the absence of standard or proper treatment protocols for kratom dependence.

In conclusion, kratom holds the potential to be developed as a treatment option for opiate dependence. It also has the potential to degenerate into a recreational drug with fatal consequences of consumption. The individual clinical case-reports emerging from the West that link kratom use to adverse reactions or fatalities almost always concerned individuals who have used kratom together with other substances. It would be unfortunate if these sporadic reports are marshalled to argue for legal sanctions against kratom. The experiences from South East Asia, on the other hand, suggest considerable potential for therapeutic use among people dependent on more severe addictive drugs. Much more scientific and social studies are required to establish its credentials as a useful drug and these calls for international collaborative studies.

Conflict of interest

The authors declare that there are no conflicts of interest.

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References

Adkins, J.E., Boyer, E.W., McCurdy, C.R., 2011. *Mitragyna speciosa*, a psychoactive tree from Southeast Asia with opioid activity. Curr. Top. Med. Chem. 11, 1165–1175.

Ahmad, K., Aziz, Z., 2012. *Mitragyna speciosa* use in the northern states of Malaysia: a cross-sectional study. J. Ethnopharmacol. 141, 446–450.

Assanangkornchai, S., Muekthong, A., Sam-Angsri, N., Pattanasattayawong, U., 2007a. The use of *Mitragyna speciosa* ('kratom'), an addictive plant, in Thailand. Subst. Use Misuse 42, 2145–2157.

Assanangkornchai, S., Pattanasattayawong, U., Samangsri, N., Mukthong, A., 2007b. Substance use among high-school students in Southern Thailand: trends over 3 years (2002–2004). Drug Alcohol Depend. 86, 167–174.
Babu, K.M., McCurdy, C.R., Boyer, E.W., 2008. Opioid receptors and legal highs: *Salvia divinorum* and kratom. Clin. Toxicol. 46, 146–152.
Boyer, E.W., Babu, K.M., Macalino, G.E., Compton, W., 2007. Self-treatment of opioid withdrawal with a dietary supplement, kratom. Am. J. Addict. 16, 352–356.
Boyer, E.W., Babu, K.M., Adkins, J.E., McCurdy, C.R., Halpern, J.H., 2008. Self-treatment of opioid withdrawal using kratom (*Mitragynia speciosa* Korth). Addiction 103, 1048–1050.
Burkill, A., 1935. A dictionary of the economic products of the Malay peninsula. 2, 1480–1483.
Cinosi, E., Martinotti, G., Simonato, P., Singh, D., Demetrovics, Z., Roman-Urrestarazu, A., Bersani, F.S., Vicknasingam, B., Piazzon, G., Li, J.-H., et al., 2015. Following the roots of kratom (*Mitragyna speciosa*): the evolution of an enhancer from a traditional use to increase work and productivity in Southeast Asia to a recreational psychoactive drug in western coutries. Biomed. Res. Int. (Article ID 968786. 11 pages).
Dorman, C., Wong, M., Khan, A., 2014. Cholestatic hepatitis from prolonged kratom use: a case report. Hepatology 61 (3), 1086–1087.
Forrester, M.B., 2013. Kratom exposures reported to Texas poison centers. J. Addict. Dis. 32 (4), 396–400.
Hassan, Z., Muzaimi, M., Navaratnam, V., Yusoff, H.M., Suhaimi, F.W., Vadivelu, R., Vicknasingam, B.K., Amato, D., Horsten, S.V., Ismail, N.I.W., et al., 2013. From kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. Neurosci. Biobehav. Rev. 37 (2), 138–151.
Havemann-Reinecke, U., 2011. Kratom and alcohol dependence: clinical symptoms, withdrawal treatment and pharmacological mechanisms—a case report. Eur. Psychiatry 26 (S1), 01–50.
Holler, J.M., Vorce, S.P., McDonough-Bender, P.C., Solomon, C.J., Magluilo Jr., J., Levine, B., 2011. A drug toxicity death involving propylhexedrine and mitragynine. J. Anal. Toxicol. 35 (1), 54–59.
Jansen, K.L.R., Prast, C.J., 1988a. Ethnopharmacology of kratom and the *Mitragyna* alkaloids. J. Ethnopharmacol. 23 (1), 115–119.
Jansen, K.L.R., Prast, C.J., 1988b. Psychoactive properties of Mitragynine (kratom). J. Psychoact. Drugs 20 (4), 455–457.
Kapp, F.G., Maurer, H.H., Auwarter, V., Winkelmann, M., Hermanns-Clausen, M., 2011. Intrahepatic cholestasis following abuse of powdered kratom (*Mitragyna speciosa*). J. Med Toxicol. 7 (3), 227–231.
Karinen, R., Fosen, J.T., Rodge, S., Vindenes, V., 2010. An accidental poisoning with mitragynine. Forensic Sci. Int. 245C, e29–e32.
Kowalczuk, A.P., Lozak, A., Zjawiony, J.K., 2013. Comprehensive methodology for identification of kratom in police laboratories. Forensic Sci. Int. 233 (1–3), 238–243.
Kronstrand, R., Roman, M., Thelander, G., Eriksson, A., 2011. Unintentional fatal intoxications with mitragynine and *O*-desmethyltramadol from the herbal blend krypton. J. Anal. Toxicol. 35 (4), 242–247.
Lee, C.T., 1957. Addiction to *Mitragyna speciosa*. Malaya. University Malaya, Kuala Lumpur In: Proceedings of the Alumni Association, 10, pp. 322–324.
McIntyre, I.M., Trochta, A., Stolberg, S., Campman, S.C., 2015. Mitragynine 'kratom' related fatality: a case report with postmortem concentrations. J. Anal. Toxicol. 39 (2), 152–155.
McWhirter, L., Morris, S., 2010. A case report of inpatient detoxification after kratom (*Mitragyna speciosa*) dependence. Eur. Addict. Res. 16 (4), 229–231.
Neerman, M.F., Frost, R.E., Deking, J., 2013. A drug fatality involving kratom. J. Forensic Sci. 58 (S1), S278–S279.
Nelsen, J.L., Lapoint, J., Hodgman, M.J., Aldous, K.M., 2010. Seizure and coma following kratom (*Mitragynina speciosa* Korth) exposure. J. Med. Toxicol. 6 (4), 424–426.
Prozialeck, W.C., Jivan, J.K., Andurkar, S.V., 2012. Pharmacology of kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. J. Am. Osteopath. Assoc. 112 (12), 792–799.
Roche, K.M., Hart, K., Sangali, B., Lefberg, J., Bayer, M., 2009. Kratom: a case of a legal high. Clin. Toxicol. 46 (7) (598).
Rosenbaum, C.D., Carreiro, S.P., Babu, K.M., 2012. Here today, gone tomorrow and back again? A review of herbal marijuana alternatives (K2, spice), synthetic cathinones (bath salts), kratom, salvia divinorum, methoxetamine, and piperazines. J. Med. Toxicol. 8 (1), 15–32.
Saingam, D., Assanangkornchai, S., Geater, A.F., Balthip, Q., 2012. Pattern and consequences of krathom (*Mitragyna speciosa* Korth.) use among male villagers in southern Thailand: a qualitative study. Int. J. Drug Policy 24 (4), 351–358.
Saingam, D., Assanangkornchai, S., Geater, A.F., Balthip, Q., 2013. Pattern and consequences of krathom (*Mitragyna speciosa* Korth) use among male villagers in southern Thailand: a qualitative study. Int. J. Drug Policy 24 (4), 351–358.
Saingam, D., Assanangkornchai, S., Geater, A.F., Lerkiatbundit, S., 2014. Vaidation of krathom (*Mitragyna speciosa* Korth) dependence scale (KDS): a dependence screen for internationally emerging psychoactive substance. Subst. Abuse 35 (3), 276–283.
Saingam, D., Assanangkornchai, S., Geater, A.F., Lerkiatbundit, S., 2016. Factor analytical investigation of krathom (*Mitragyna speciosa* Korth) withdrawal syndrome in Thailand. J. Psychoact. Drugs 25, 1–10.
Schmidt, M.M., Sharma, A., Schifano, F., Feinmann, C., 2011. Legal highs on the net-evaluation of UK-based websites, products and product information. Forensic Sci. Int. 206 (1–3), 92–97.
Sheleg, S.V., Collins, G.B., 2011. A coincidence of addiction to kratom and severe primary hypothyroidism. J. Addict. Med. 5 (4), 300–301.
Singh, D., Muller, C.P., Vicknasingam, B.K., 2014. Kratom (*Mitragyna speciosa*) dependence, withdrawal symptoms and craving in regular users. Drug Alcohol Depen. 139, 132–137.
Singh, D., Muller, C.P., Vicknasingam, B.K., Mansor, S.M., 2015. Social functioning of kratom (*Mitragyna speciosa*) users in Malaysia. J. Psychoact. Drugs 47 (2), 125–131.
Suwanlert, S., 1975. A study of kratom eaters in Thailand. Bull. Narcot. 27 (3), 21–27.
Swogger, M.T., Hart, E., Erowid, F., Erowid, E., Trabold, N., Yee, K., Parkhurst, K.A., Priddy, B.M., Walsh, Z., 2015. Experiences of kratom users: a qualitative analysis. J. Psychoact. Drugs 47 (5), 360–367.
Tanguay, P., 2011. Kratom in Thailand, decriminalisation and community control. Series on legislative reform of drug policies Nr. 13. Transnational Institute. International Drug Policy Consortium (IDPC).
Trakulsrichai, S., Tongpo, A., Sriapha, C., Wongvisawakorn, S., Rittilert, P., Kaojarern, S., Wananukul, W., 2013. Kratom abuse in ramathibodi poison center, Thailand. A five-year experience. J. Psychoact. Drugs 45 (5), 404–408.
Tungtananuwat, W., Lawanprasert, S., 2010. Fatal 4 × 100; home-made kratom juice cocktail. J. Health Res. 24 (1), 43–47.
Vicknasingam, B., Narayanan, S., Goh, T.B., Mansor, S.M., 2010. The informal use of ketum (*Mitragyna speciosa*) for opioid withdrawal in the northern states of peninsular Malaysia and implications for drug substitution therapy. Int. J. Drug Policy 21 (4), 283–288.
Warner, M.L., Kaufman, N.C., Grundmann, O., 2016. The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. Int. J. Legal Med. 130 (1), 127–138.