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Invited review

The medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse

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ABSTRACT

The leaves of *Mitragyna speciosa* (commonly known as kratom), a tree endogenous to parts of Southeast Asia, have been used traditionally for their stimulant, mood-elevating, and analgesic effects and have recently attracted significant attention due to increased use in Western cultures as an alternative medicine. The plant's active alkaloid constituents, mitragynine and 7-hydroxymitragynine, have been shown to modulate opioid receptors, acting as partial agonists at mu-opioid receptors and competitive antagonists at kappa- and delta-opioid receptors. Furthermore, both alkaloids are G protein-biased agonists of the mu-opioid receptor and therefore, may induce less respiratory depression than classical opioid agonists. The *Mitragyna* alkaloids also appear to exert diverse activities at other brain receptors (including adrenergic, serotonergic, and dopaminergic receptors), which may explain the complex pharmacological profile of raw kratom extracts, although characterization of effects at these other targets remains extremely limited. Through allometric scaling, doses of pure mitragynine and 7-hydroxymitragynine used in animal studies can be related to single doses of raw kratom plant commonly consumed by humans, permitting preliminary interpretation of expected behavioral and physiological effects in man based on this preclinical data and comparison to both anecdotal human experience and multiple epidemiological surveys. Kratom exposure alone has not been causally associated with human fatalities to date. However, further research is needed to clarify the complex mechanism of action of the *Mitragyna* alkaloids and unlock their full therapeutic potential.

Contents

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1. Introduction

1.1. Background and significance

The leaves of the psychoactive plant *Mitragyna speciosa* (Fig. 1A), known commonly as “kratom” in Thailand, or “biak biak” in Malaysia, have been used by humans in Southeast Asia for centuries to treat a variety of ailments. The plant material is typically consumed directly or as a tea. At low doses, kratom is primarily used for its stimulating effects. At higher doses, opioid-like effects are present, and the plant is used as a general analgesic, and as a substitute for opium or to treat opium withdrawal symptoms. Kratom's mood-elevating effects have also raised concerns about the plant's potential for misuse as an addictive recreational drug, and legal controls have been instituted in some regions. However, to date there have been no fatalities that can be solely attributed to kratom overdose. Other medicinal applications are also known, including use as a treatment for fever, cough, diarrhea, depression, and anxiety (Adkins et al., 2011; Matsumoto, 2006; Raffa et al., 2013; Takayama, 2004; Takayama et al., 2002). In the past decade, use of kratom has expanded significantly in the United States. This growing interest, combined with the explosion of social media, has considerably increased the anecdotal knowledge base related to kratom's efficacy in treating a large variety of medical conditions. Importantly, favorable reports in treatment of intractable pain syndromes and substance use disorders suggest the potential of kratom to address multiple areas of unmet medical need. Accordingly, the study of kratom is of high relevance to public health and has resulted in a number of scientific reviews in recent years (Hassan et al., 2013; Prozialeck et al., 2012; Suhaimi et al., 2016; Warner et al., 2016)

The present review aims to place both recent and historical observations concerning the behavioral and physiological effects of kratom in man into the context of the most up-to-date knowledge of the molecular pharmacology of kratom alkaloids. Similarly, an attempt is made to rationally link animal studies with human experience through dose correlation and critical analysis. Lastly, we aim to highlight key aspects of the field that remain underexplored, with the goal of guiding future research.

2. Molecular constituents

2.1. Major alkaloids

In light of its well-documented medicinal properties, the molecular constituents of kratom have been extensively studied, with more than 40 unique indole alkaloids having been identified in the plant (Adkins et al., 2011; León et al., 2009; Shellard, 1974; Takayama, 2004). Among these, the indole alkaloid mitragynine (Fig. 1B) has been universally cited as the primary alkaloid constituent of kratom, accounting for up to 66% by mass of crude alkaloid extracts (Shellard, 1974; Takayama, 2004). This alkaloid was first isolated in 1921 and the structure assigned in the 1960s by chemical and crystallographic means (Field, 1921; Zacharias et al., 1965). The other major alkaloids of kratom are paynantheine, speciogynine, and speciociliatine (Fig. 1C) (Shellard, 1974). The quantities of these four major alkaloids are subject to significant variation among different regional varieties of the plant, and are also dependent on plant age, findings that considerably complicate the interpretation of reported psychoactive and medicinal effects from the raw plant material (Adkins et al., 2011; León et al., 2009; Shellard, 1974.; Takayama, 2004). Among the various minor alkaloids, the oxidized derivative 7-hydroxymitragynine (7-OH) (Fig. 1C) is of particular interest, as it has been reported to exhibit analgesic effects mediated through agonist activity at the mu-opioid receptor (MOR) exceeding in potency those of the prototypical opioid agonist morphine (Matsumoto et al., 2004; Ponglux et al., 1994)

2.2. Alkaloid content of raw plant

Kratom is readily available for purchase from a large number of internet vendors, most commonly as dried and powdered leaves. Two reports have quantified mitragynine and 7-OH in such commercial kratom preparations by liquid chromatography-mass spectrometry (LC-MS) methods (Kikura-Hanajiri et al., 2009; Lydecker et al., 2016). A compilation and analysis of these results is presented in Table 1. The term “leaf” refers to products described as dried leaves, while “powder” refers to products obtained in a

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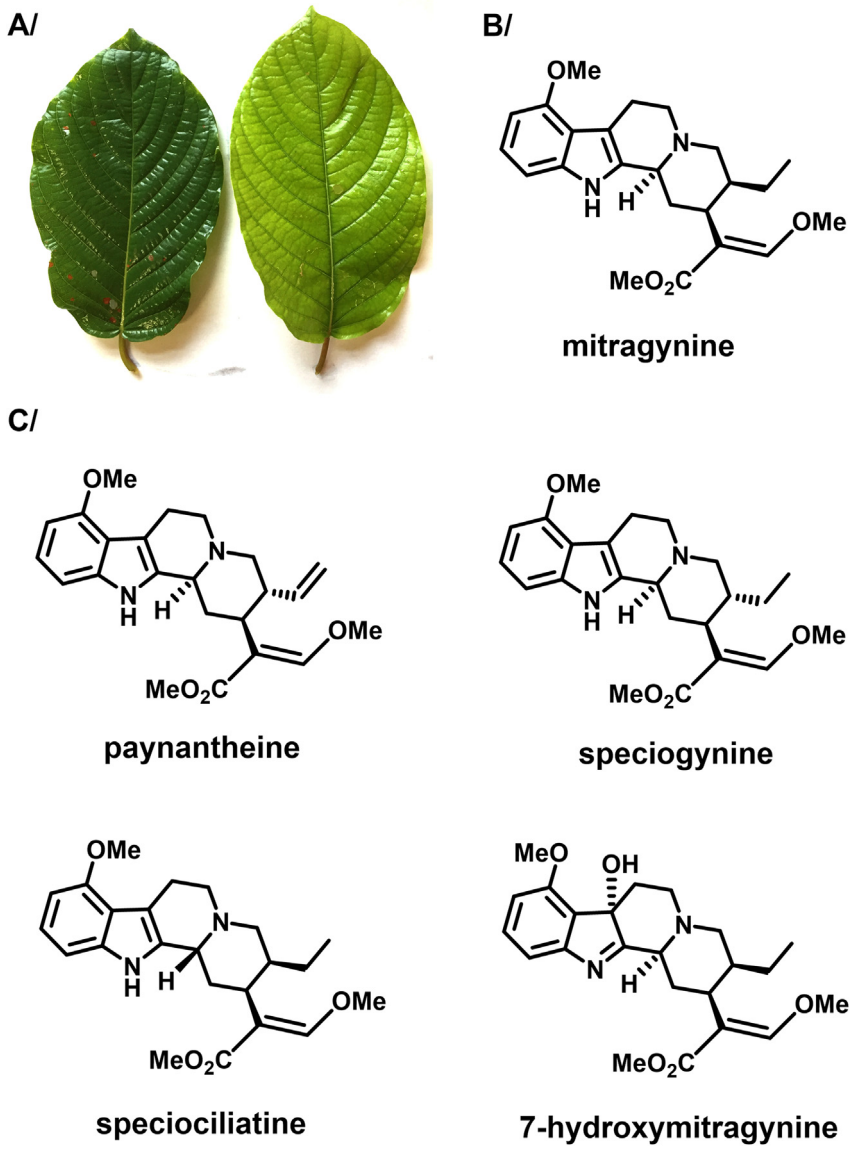

Fig. 1. (A) Leaves of *Mitragyna speciosa* (kratom); (B) Structure of mitragynine; (C) Structure of other major kratom alkaloids.

pre-ground form, either loose or encapsulated (presumably representing simple dried and ground *Mitragyna speciosa* leaf, although this cannot be verified). Products described as extracts, resins, or mixtures with other botanicals in these studies are excluded from the present analysis, as their methods of preparation and origins are likely to be too varied to draw meaningful conclusions regarding the typical potency of such products on the broader market. It should be noted however, that none of these more ill-defined products contained 7-OH at concentrations higher than simple leaf material. Overall, the mean observed concentrations are quite consistent across products and reports, with mean concentrations of mitragynine in the range of ~1.5–2 mass% and 7-OH in the range of ~0.02–0.03 mass% (based on dry leaf weight). Accordingly, the mitragynine concentration in most kratom products is 50- to 100-fold higher than the 7-OH concentration. Concentrations of 7-OH in powdered products are also found to be marginally higher than in leaf products, but the significance of this observation is questionable given the large product-to-product variability and limited data points available.

Approximate concentrations of mitragynine and 7-OH in raw

Table 1
Average mass% of mitragynine and 7-OH in raw kratom leaf or powder.

Reference	Mass% ± STD			
	mitragynine (leaf)	mitragynine (powder)	7-OH (leaf)	7-OH (powder)
Kikura-Hanajiri et al., 2009	1.80 ± 0.51	2.02 ± 0.13	0.0196 ± 0.010	0.0286 ± 0.0099
Lydecker et al., 2016	–	1.67 ± 0.28	–	0.0328 ± 0.0093
	Combined Ave = 1.80 ± 0.36		**Combined Ave = 0.0273 ± 0.014**	

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leaf have also been determined by extraction and purification of the pure alkaloids (Ponglux et al., 1994). In this case, the 7-OH content (0.026 mass%) was within the typical range as determined by the LC-MS studies, while the mitragynine content (0.86 mass%) was significantly lower, but this may be due to poor extraction/purification efficiency. Unfortunately, to our knowledge no study has rigorously quantified the content of the other major alkaloids (paynantheine, speciogynine, and speciociliatine) across different kratom products, complicating interpretations of their influence on kratom pharmacology. However, one study has reported that extraction of powdered kratom leaf yielded a combined ~0.5–0.7 mass% for these three alkaloids, suggesting that their potential involvement in kratom's effects should not be ignored (Kruegel et al., 2016). Thus, it is necessary to recognize that the effects of kratom leaf, powder, or extracts are expected to diverge widely from both the pure *Mitragyna* alkaloids themselves and classical MOR agonists, based on variable concentrations of mitragynine, 7-OH, and minor alkaloids depending on area and time of harvest, and the potential contribution of other *Mitragyna* alkaloids and as-yet-unknown substances in the plant.

3. *In vitro* pharmacology

3.1. Opioid pharmacology

3.1.1. Mu-opioid receptor

The major kratom alkaloids have recently been profiled for binding and functional activity at the human and rodent opioid receptors (Kruegel et al., 2016). Using radioligand displacement assays in transfected cells, binding affinities at the human MOR (hMOR) were determined for mitragynine ($K_i = 233$ nM) and 7-OH ($K_i = 47$ nM). In bioluminescence resonance energy transfer (BRET) functional assays at hMOR, mitragynine exhibited low efficacy partial agonist activity ($E_{max} = 34\%$, relative to [D-Ala^2, NMe-Phe^4, Gly-ol^5]-enkephalin, DAMGO) with an EC_{50} of 339 nM. Similarly, 7-OH was a partial agonist at hMOR ($E_{max} = 47\%$), but with higher potency ($EC_{50} = 35$ nM). The other major alkaloids, specifically paynantheine, speciogynine, and speciociliatine, were found to exhibit competitive antagonist activity at hMOR with IC_{50} values in the micromolar range. Accordingly, it may be expected that the overall hMOR activity of raw kratom plant or extracts is a complex interplay of competing agonist and antagonist effects, dependent on the mixture of alkaloids present. As a point of reference, the prototypical MOR agonist morphine is a potent full agonist in these same functional assays ($EC_{50} = 3$ nM) and thus, *in vitro*, 7-OH and mitragynine are 10- and 100-fold less potent than morphine at hMOR, respectively (Andrew Kruegel, unpublished data).

This same study also reported comparable binding affinities at mouse MOR (mMOR) for mitragynine ($K_i = 230$ nM) and 7-OH ($K_i = 37$ nM). However, in functional assays with mMOR, interspecies variation was observed, with mitragynine acting as a competitive antagonist, while 7-OH retained its partial agonist activity, although with lower efficacy ($EC_{50} = 38$ nM; $E_{max} = 23\%$) (Kruegel et al., 2016). However, another recent report using a different assay method ([^{35}S]GTPγS displacement) did demonstrate partial agonist activity with mitragynine at mMOR ($E_{max} = 65\%$; $EC_{50} = 203$ nM), while results with 7-OH were similar ($E_{max} = 77\%$; $EC_{50} = 53$ nM) (Váradi et al., 2016). Likewise, an earlier report that studied binding in guinea pig brain homogenates reported a similar affinity for 7-OH ($K_i = 13$ nM), but a much higher binding affinity for mitragynine ($K_i = 7.2$ nM) (Takayama et al., 2002). These interspecies and interassay differences necessarily complicate the application of this *in vitro* data for interpreting *in vivo* findings in animals or man. Further, since actual brain concentrations of mitragynine and 7-OH have not been studied, it is not possible to correlate potency *in vitro* to expected receptor occupancy at various dose levels.

3.1.2. Kappa- and delta-opioid receptor

The activity of the major *Mitragyna* alkaloids have also been profiled at the human kappa-opioid receptor (hKOR) and human delta-opioid receptor (hDOR) (Kruegel et al., 2016). Both mitragynine and 7-OH bind to hKOR (K_i mitragynine = 772 nM; K_i 7-OH = 188 nM) and in functional assays, act as competitive antagonists with IC_{50} values in the micromolar range. In the case of hDOR, binding was observed for 7-OH ($K_i = 219$ nM), but was negligible for mitragynine ($K_i > 10$ μM), while both alkaloids exhibited only weak antagonist activity in functional assays at this receptor ($IC_{50} > 10$ μM). Interspecies and interassay differences have again been observed at these receptors. For example, reported affinities of mitragynine for mouse DOR in transfected cells ($K_i = 1.0$ μM) and DOR in guinea pig brain ($K_i = 60$ nM) are much stronger than observed with the human receptor (Kruegel et al., 2016; Takayama et al., 2002; Váradi et al., 2016). Similarly, for 7-OH, submicromolar mDOR antagonism has been demonstrated in the [^{35}S]GTPγS displacement assay (Váradi et al., 2016). Therefore, the contribution of KOR and DOR antagonism to kratom's *in vivo* effects remains unclear at this time.

3.1.3. Biased signaling at MOR

The activation of hMOR induced by both mitragynine and 7-OH has been shown to be biased toward G protein signaling and neither alkaloid recruits β-arrestin to a measurable degree (Kruegel et al., 2016). This observation may be of relevance in explaining the apparently superior side effect profile of kratom (as well as mitragynine and 7-OH, see below) compared to classical opioid agonists, particularly in regard to respiratory depression and constipation. Animal studies and early human data have suggested that G protein-biased MOR agonists may induce less respiratory depression and inhibition of gastrointestinal transit compared to classical opioids, which activate both the G protein and β-arrestin signaling pathways (Siuda et al., 2017). Further studies should address the potential for mitragynine and 7-OH derivatives to provide analgesia without significant respiratory depression or constipation due to G protein-biased signaling.

3.2. Non-opioid pharmacology

A number of studies have implicated non-opioid receptors in the actions of mitragynine. This compound has been shown to bind to some degree to several non-opioid central nervous system (CNS) targets, including alpha-2 adrenergic receptors (α2R), adenosine A_{2a} receptors, dopamine D_2 receptors, and the serotonin receptors 5-HT_{2C} and 5-HT_7, but the strength of these affinities has not been reported (Boyer et al., 2008). Mitragynine analgesia has also been shown to be inhibited by the α2R antagonist idazoxan, and by the non-specific serotonin antagonist cyproheptadine (Matsumoto et al., 1996a). However, another study showed that in a cell line expressing α2R, mitragynine did not act directly as an agonist of this receptor (Tohda et al., 1997). Accordingly, there remains uncertainty regarding the importance of other CNS receptors in mediating mitragynine's effects. Furthermore, there are no reports concerning the pharmacology of the other major kratom alkaloids (paynantheine, speciogynine, and speciociliatine). Considering that together, these three alkaloids often constitute 0.5–0.7 mass% of raw kratom (in total, almost as much as mitragynine itself), a better understanding of their molecular targets is essential to understanding this plant.

Conflicting antagonism studies with nalorphine have also been conducted *in vivo*. Oddly, certain behavioral effects of mitragynine

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(e.g. mydriasis in cats) were reversed by this treatment, while others (e.g. analgesia in rats) were not (Macko et al., 1972). However, given more recent studies demonstrating antagonism of mitragynine analgesia by naloxone (Matsumoto et al., 1996b), and the fact that nalorphine is actually a partial opioid agonist (Paul et al., 1991), these findings should be taken with reservation. It seems more likely that the analgesic effects of oral (p.o.) mitragynine are indeed opioid mediated (see below). Since little is known about the molecular targets of other *Mitragyna* alkaloids or compounds present in kratom, further studies are required to elucidate the molecular mechanisms of potentially non-opioid antidepressant and stimulating effects reported for kratom at lower doses.

3.3. Synthesis and structure-activity relationships

The mitragynine molecular scaffold has been explored through both total and partial synthesis of the natural products and a number of analogs (Jun Ma et al., 2007; Kerschgens et al., 2012; Kruegel et al., 2016; Ma et al., 2009; Takayama et al., 2002, 1995). This work has afforded a preliminary understanding of the structural determinants of MOR activity in this scaffold (Fig. 2). As a whole, the known structure-activity relationships (SAR) for mitragynine and 7-OH define a pharmacophore that is fairly intolerant to structural modification, with small changes, particularly to the acrylate and ethyl groups on ring D, being sufficient to abolish opioid activity. Further, demethylation of the aryl methoxy group to give phenolic analogs reduces the potency of both mitragynine and 7-OH at MOR, in contrast to morphinan-based opioids, where such a change greatly enhances potency. In combination with molecular docking, this SAR suggests that mitragynine and its analogs adopt a distinct binding pose in the pocket of the MOR (Kruegel et al., 2016). Additional studies are needed to explore the SAR of mitragynine and 7-OH in more detail and also the other alkaloids, if and when their molecular targets are identified. Likewise, the field would benefit from further development of robust synthetic methods to access the mitragynine scaffold, particularly if such approaches are amenable to rapid structural diversification or large-scale synthesis.

4. *In vivo* pharmacology and toxicology in animals

The behavioral and physiological effects of both kratom extracts and pure alkaloids have been studied in a number of animal species. As a whole, these studies have placed a particular emphasis on kratom's analgesic effects and confirmation of the purported opioid mechanism *in vivo*. Some work has also been directed towards quantification of kratom's addictive potential.

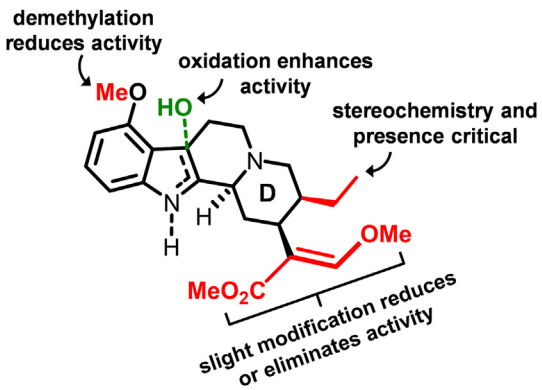

Fig. 2. Key structure-activity relationships of the mitragynine and 7-OH molecular scaffolds.

4.1. Analgesic effects

4.1.1. Analgesic studies with kratom extracts

A number of reports have demonstrated the analgesic activity of kratom extracts (both crude alcohol extract and mixed alkaloid fractions) in rodents (Carpenter et al., 2016; Reanmongkol et al., 2007; Sabetghadam et al., 2010, 2013a; Shaik Mossadeq et al., 2009). A selection of key results from these studies are collected in Table 2. Overall, both the alcohol extract and crude alkaloid fraction of kratom are low potency analgesics in several rodent models. By the oral route, typical active doses are >50 mg/kg for the alcohol extract and >20 mg/kg for the alkaloid fraction. In all cases where it was examined, naloxone inhibited or reversed the observed analgesic effects, indicating that said effects of kratom alkaloids are at least partially mediated by opioid receptors. However, available studies should be considered incomplete for several reasons. First, the alkaloid content and composition of the extracts used are not typically analyzed or standardized and thus, it is difficult to correlate these studies using complex mixtures, to the complementary data available with pure alkaloids (see below). Second, most of these studies do not study a complete dosage range and thus, the analgesic potency of kratom extracts in animals remains poorly defined.

4.1.2. Analgesic studies with mitragynine

A number of reports have demonstrated the analgesic activity of pure mitragynine in multiple animal species and tests (Carpenter et al., 2016; Macko et al., 1972; Matsumoto et al., 1996b; Matsumoto, 2006; Sabetghadam et al., 2013a). Key results from these studies are presented in Table 2. The most extensive investigations were conducted by Macko and colleagues, who studied the analgesic activity of mitragynine in mice, rats, and dogs (Macko et al., 1972). In all species, mitragynine was an active analgesic when given p. o. or intraperitoneally (i.p.), with potency comparable to codeine. Oddly, mitragynine was largely inactive in both mice and rats when administered subcutaneously (s.c.). A similar dependence on route of administration may also be inferred by examination of later reports (Carpenter et al., 2016; Matsumoto et al., 1996b; Matsumoto, 2006). This unusual observation suggests that an active metabolite, formed most efficiently during first-pass metabolism following p. o. or i. p. administration, may be involved in mediating the analgesic activity of mitragynine. However, this hypothesis is conflicted by the finding that mitragynine is also active by intracerebroventricular (i.c.v) administration (Matsumoto et al., 1996b), where hepatic metabolism would not be expected to play a major role. Therefore, the potential involvement of metabolites or pharmacokinetics (PK) in the analgesic actions of mitragynine remains unclear and warrants further study.

4.1.3. 7-OH analgesia and side effects

Several reports have described potent analgesia elicited by 7-OH in mice (Matsumoto et al., 2008, 2004) (summarized in Table 3). In mice, this compound is approximately 4- to 5-fold more potent than morphine via s.c. administration and 10- to 20-fold more potent by the oral route (due to morphine's poor oral bioavailability) (Matsumoto et al., 2008). The analgesic effects of 7-OH have also been demonstrated to be opioid mediated through antagonism studies with naloxone and exhibit tolerance development similar to morphine (Matsumoto et al., 2005). However, 7-OH induces less inhibition of GI transit than morphine in mice (Matsumoto et al., 2008). Therefore, 7-OH represents a potential starting point for the development of new opioid analgesics with reduced side effects. Unfortunately, no toxicological data is available for 7-OH and its potential to induce other well-known opioid side effects, most importantly respiratory depression, has also not been quantified.

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Table 2
Summary of analgesic activity of kratom extracts and pure mitragynine.

Substance	Reference	Species	Dose/Route[a]	Test	ED_{50} (mg/kg)[b]	Naloxone Reversal[c]
Alcohol Extract	Carpenter et al., 2016	Rat	300 mg/kg, i.p.	hot plate	inactive	–
			300 mg/kg, p.o.	hot plate	inactive	–
	Shaik Mossadeq et al., 2009	Mouse	i.p.	writhing	>100	–
			i.p.	hot plate	>50	yes
		Rat	i.p.	formalin	>100	–
	Sabetghadam et al., 2010	Rat	p.o.	hot plate	>200	yes
			p.o.	tail flick	>100	yes
	Reanmongkol et al., 2007	Mouse	p.o.	hot plate	>50	yes
		Rat	p.o.	tail flick	inactive at 200	–
Crude Alkaloid Extract	Carpenter et al., 2016	Rat	75 mg/kg, i.p.	hot plate	inactive	–
	Sabetghadam et al., 2010	Rat	p.o.	hot plate	>10	yes
			p.o.	tail flick	>20	yes
	Reanmongkol et al., 2007	Mouse	p.o	hot plate	>20	yes
		Rat	p.o.	tail flick	inactive at 20	–
	Sabetghadam et al., 2013a	Mouse	p.o.	hot plate	194	–
Mitragynine	Carpenter et al., 2016	Rat	30 mg/kg, i.p.	hot plate	active	–
			100 mg/kg, p.o.	hot plate	active	–
	Matsumoto et al., 1996b	Mouse	i.p.	tail pinch	>10	yes
			i.p.	hot plate	>30	yes
			i.c.v.	tail pinch	>1 μg/mouse	yes
			i.c.v.	hot plate	>3 μg/mouse	yes
	Matsumoto, 2006	Mouse	s.c.	tail flick	>60	–
	Sabetghadam et al., 2013a	Mouse	p.o.	hot plate	22	–
	Macko et al., 1972[e]	Mouse	92 mg/kg, s.c.	hot plate	inactive	–
			92 mg/kg, p.o.	hot plate	100% analgesia	–
		Rat	s.c.	tail flick	>31	–
			i.p.	tail flick	14.4	–
			p.o.	tail flick	17.8	no[d]
			p.o.	paw inflam.	16.8	–
		Dog	p.o.	thermal	~4-8	–

[a] When no dose given, multiple doses were examined in the study.
[b] When no ED_{50} was given, value of >X indicates the minimum dose, X, eliciting detectable analgesia.
[c] "-" indicates not tested.
[d] Using nalorphine.
[e] ED_{50}s have been corrected for counterion mass to reflect freebase values.

Table 3
Analgesic activity of 7-OH in mice.

Reference	Test	Analgesic ED_{50} (mg/kg)	
		s.c.	p.o.
Matsumoto et al., 2004[a]	tail flick	3	5
	hot plate	2.5	13
Matsumoto et al., 2008	tail flick	0.80	4.4
	hot plate	0.93	2.2

[a] ED_{50}s are estimated from provided dose-response curves.

4.2. Toxicology

4.2.1. Toxicology of kratom extracts

The toxic effects of kratom extracts have been studied. For total alkaloid extracts in mice, p. o. LD_{50}s of 173 mg/kg (Reanmongkol et al., 2007) and 592 mg/kg (Sabetghadam et al., 2013b) were found. For methanolic extracts in mice, a p. o. LD_{50} of 4900 mg/kg has been reported (Reanmongkol et al., 2007). After 14-day p. o. treatment with methanol extract at 100, 500, and 1000 mg/kg, rats showed mild nephrotoxicity and more moderate hepatotoxicity, which were severe at the highest dose, although no significant changes in hematology, organ weights, body weights, food and water consumption, or gross behavior were noted (Harizal et al., 2010). Similarly, 28-day p. o. exposure to methanol extract at 100, 200, and 500 mg/kg also produced biochemical and histopathological signs of liver and kidney toxicity but no hematological changes (Ilmie et al., 2015). It should be mentioned however, that morphine induces similar toxicological signs at sufficiently high doses, so the relevance of these findings with extracts to the toxicity of raw kratom or the pure alkaloids at therapeutic doses remains uncertain.

4.2.2. Mitragynine side effects and acute toxicity

Macko and colleagues also report on a number of gross behavioral effects and negative side effects elicited by mitragynine, with several measures demonstrating a clear distinction between mitragynine and the classical opioid codeine (a prodrug of morphine). Respiratory depression was either nonexistent or significantly attenuated relative to codeine and morphine in cats (i.p.) and relative to codeine in anesthetized (intravenous, i. v.) and unanesthetized (p.o.) dogs. Likewise, by the oral route, codeine elicited emesis in dogs, while mitragynine did not. Mitragynine induced only slight inhibition of GI transit (<20%) in rats by both p. o. and i. p. routes, while codeine produced more significant inhibition by both routes (Macko et al., 1972). However, mitragynine cessation after chronic administration in rats did induce a withdrawal syndrome in a more recent study (Yusoff et al., 2016).

Qualitative observations by Macko also revealed that mitragynine given p. o. or i. p. produced only mild disturbances in gross behavior in rats (807 mg/kg, p. o.) and cats (46 mg/kg, i. p.), and no notable effects in dogs (80 mg/kg, p. o.). Likewise, in Rhesus monkeys, mitragynine did not elicit notable behavioral effects by the oral route (46 mg/kg). In contrast, i. v. administration of mitragynine evoked pronounced negative side effects in cats, dogs, and monkeys, including respiratory depression, convulsions, and in one cat, death (Macko et al., 1972). The reasons for this contrast in side

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effects depending on route of administration remain unclear, but recapitulate the similar dependence of analgesic potency on delivery route (see above) and may be related to first-pass metabolism. Sabetghadam also observed low acute toxicity for mitragynine administered orally in mice, reporting an LD_{50} of 477 mg/kg (Sabetghadam et al., 2013a). In contrast, death of a single rat at the lower dose of 200 mg/kg p. o. has been described, but no further details were provided (Janchawee et al., 2007).

Overall, mitragynine appears to act as an atypical opioid receptor agonist *in vivo* when administered p. o., with an improved side effect profile compared to classical morphinan-based opioids and limited toxicity following acute administration at reasonable doses.

4.2.3. Mitragynine chronic toxicology

Macko and colleagues also profiled the toxicity of mitragynine following chronic administration in rats and dogs. In rats receiving mitragynine at 4 or 40 mg/kg/day p.o., 5 days per week for 6 weeks, minor changes in body weight and liver and kidney weights were observed, but no other behavioral or physiological side effects were noted. In dogs, no adverse effects were observed after 3 weeks of dosing at 5 or 20 mg/kg/day p.o. however, an additional 3-week dosing period at 40 mg/kg/day p.o. in the high-dose dogs resulted in changes in blood chemistry (that reversed on drug withdrawal), liver cell morphology, and lymphatic hyperplasia (Macko et al., 1972). Sabetghadem observed similar results in rats, with low (1 mg/kg/day, p.o.) and intermediate (10 mg/kg/day, p.o.) doses showing little sign of toxicity, but a higher dose (100 mg/kg/day, p.o.) inducing hematological and liver and brain histopathological changes suggestive of toxicity (Sabetghadam et al., 2013b). Accordingly, additional chronic toxicology studies are indicated to further explore the negative effects observed at higher doses and further define a safe dose ceiling for chronic administration in humans. It should also be noted that toxicological studies with pure mitragynine are of limited relevance to current patterns of human use, where alkaloids are often consumed in the matrix of raw plant matter and the actual systemic exposure to those alkaloids remains poorly defined following this type of administration (for further discussion, see below, ADME and Pharmacokinetics).

4.3. Other therapeutic effects of kratom alkaloids

Mitragynine and morphine via p. o. administration were equipotent cough suppressants in dogs (Macko et al., 1972). In rodents, both mitragynine and kratom extracts have demonstrated antidepressant-like activity in the forced swim test and anxiolytic-like activity in the elevated plus maze (Hazim et al., 2014; Idayu et al., 2011; Kumarnsit et al., 2007; Mohamad et al., 2013; Yusoff et al., 2016).

4.4. Animal studies of abuse potential

Given their opioid actions, several studies have examined the abuse potential of kratom and its alkaloids in classical animal models. In a conditioned place preference (CPP) paradigm in rats, mitragynine exhibited reinforcing effects following repeated dosing at 10 and 30 mg/kg i.p. (Yusoff et al., 2016). These same investigators later showed that the acquisition of this mitragynine-induced CPP at 10 mg/kg i.p. was inhibited by naloxone (0.3 or 1 mg/kg s.c.), suggesting an opioid-dependent effect (Yusoff et al., 2017). Similarly, another study demonstrated CPP in rats at 5 and 30 mg/kg i.p., but not at an intermediate dose of 10 mg/kg i.p. (Sufka et al., 2014). Mitragynine (15 mg/kg, i.p.) has also been shown to substitute for morphine in a discriminative stimulus paradigm in rats (Harun et al., 2015). In the case of 7-OH, CPP and motor stimulation are observed in mice at a dose of 2 mg/kg s.c. (Matsumoto et al., 2008), and the compound substitutes for morphine at 3 mg/kg i.p. in rats (Harun et al., 2015). These results are certainly concerning, especially for mitragynine, where the dosing corresponds to levels of exposure expected to be achievable with reasonable doses of kratom (for 7-OH, these doses are well above expected human exposures, see below). However, the oral bioavailability of mitragynine is low and the PK profile following i.p. administration is not known (see below), but is expected to present greater concentrations of mitragynine to the systemic circulation (compared to p.o.). Considering this, in combination with the stark differences in effects observed by Macko depending on administration route, care should be taken in correlating these results to man. Further, the Sufka study also reported that crude alcohol and alkaloid extracts of kratom did not induce CPP in rats at doses of 300 and 75 mg/kg i.p., respectively (Sufka et al., 2014). Notably, similar doses of such extracts have also been shown to induce analgesic effects in rats, and thus, kratom extracts appear to achieve analgesic activity with limited reinforcement. This observation highlights the difficulty in correlating animal studies using pure alkaloids, often delivered by parenteral routes, to experience in man, where oral use of raw kratom or its extracts is the most common method of use. The complex mixture of alkaloids present in the kratom plant may present a polypharmacological activity profile that has less potential for abuse, the mitragynine content of the extracts may be too low, or pharmacokinetic differences between oral and parenteral routes attenuate reinforcing effects. These observations are also consistent with both the mixed agonist and antagonist activity of the major kratom alkaloids at the opioid receptors and potentially, the other non-opioid receptor activities observed *in vitro* (see above). The US Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), has published a guidance on the "Assessment of Abuse Potential for Drugs" which includes a battery of tests that should be performed before a drug can be deemed abuse liable (FDA, 2017). Although both CPP and drug discrimination studies have been conducted for kratom and its alkaloids, the route of administration and doses may not adequately reflect human use. In addition, other tests such as the Irwin and motor performance tests, physical dependence assessment, and self-administration studies have not been reported to date following oral administration in doses comparable to those used by humans. A recent 8-factor analysis of abuse potential conducted according to the requirements of the Controlled Substances Act estimated the doses of oral kratom required in a 70-kg human to achieve either reinforcing effects or substitution for morphine as 200 g and 630 g, respectively, because of the low oral bioavailability of mitragynine (Pinney Associates, 2016). From the preceding discussion, it should be clear that the current body of knowledge in regard to potential kratom and *Mitragyna* alkaloid abuse liability is at best in its infancy and requires gathering both more animal and human data for clarification.

5. ADME and pharmacokinetics

5.1. In vitro ADME

One study has evaluated mitragynine and 7-OH in several *in vitro* assays of absorption, distribution, metabolism, and excretion (ADME) (Manda et al., 2014). Both mitragynine and 7-OH were partially degraded in simulated gastric fluid (~25% after 2 h) but stable in simulated intestinal fluid. Both mitragynine and 7-OH exhibited moderate to high apparent permeability coefficients (P_{app}) and efflux ratios of ~1 (not effluxed by P-gp) in both Caco-2 and MDR1-MDCK cell models, suggesting that both compounds have the potential for significant GI absorption and

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blood-brain barrier (BBB) penetration via passive diffusion. Mitragynine was fairly stable in both human liver microsomes and S9 fractions ($t_{1/2}$ > 2 h), while 7-OH was rapidly metabolized ($t_{1/2}$ = 24 min) in microsomes, but more stable in S9 fractions without NADPH ($t_{1/2}$ > 2 h, Phase II metabolism only). This study also demonstrated high plasma protein binding (>90%) and weak inhibition of P-gp (IC_{50} > 15 μM) for both compounds. Another report showed that mitragynine is also stable in plasma (Parthasarathy et al., 2010). Overall, this *in vitro* data is consistent with favorable drug-like properties for a brain-penetrant analgesic and is an acceptable starting point to develop new drugs based on these lead scaffolds. Two studies have demonstrated that extracts of kratom (both methanolic and crude alkaloid fractions) are fairly potent inhibitors of CYP3A4 and CYP2D6 *in vitro* (Hanapi et al., 2010; Kong et al., 2011). Accordingly, there exists the potential for kratom to precipitate unfavorable interactions with other drugs metabolized through these enzymes. These observations should be confirmed *in vivo* and efforts made to identify the specific alkaloids responsible for the observed bioactivity. Likewise, there exists the possibility for the gross behavioral effects of kratom to differ from the pure alkaloids based not only on polypharmacology (see above), but also on metabolic interactions between the mixed alkaloids.

5.2. Pharmacokinetics of mitragynine

Several studies have examined the PK of mitragynine in rats (de Moraes et al., 2009; Janchawee et al., 2007; Parthasarathy et al., 2010; Vuppala et al., 2011) and a single study has been conducted in humans (Trakulsrichai et al., 2015). The results of these studies are summarized in Table 4. By the oral route in rats, all studies are consistent, demonstrating intermediate half-life ($t_{1/2}$ > 3 h) and T_{max}, a high apparent volume of distribution (V_d/F), and linear dose-response. By the i.v. route, the two available studies provide conflicting results for several PK parameters. However, the data clearly indicates that the oral bioavailability (F) of mitragynine in rats is modest or low (<25% and possibly as low as 3%). The single human study is difficult to interpret because 1) the subjects were chronic consumers of kratom, 2) PK was studied following stabilization on a repeated daily dose, 3) subjects were given different dose levels with small groups sizes (n = 1–3) at each dose, and 4) the mitragynine dose was delivered in the form of kratom tea, not as a pure compound. Nevertheless, this report tentatively suggests a long half-life (23.2 h) for mitragynine in man following p.o. administration. V_d/F was also very high, consistent with the rat studies, suggesting similar low oral bioavailability. For one subject receiving a dose of ~0.3 mg/kg p.o., max concentration (C_{max}) and area under the curve ($AUC_{(0\rightarrow inf)}$) were also provided and were of the same order of magnitude as would be expected in rats at an equivalent estimated dose (~1.8 mg/kg, p.o. in rats by allometric scaling, see below). The observed C_{max} in this subject corresponds to a plasma concentration of 260 nM. Considering that higher doses of kratom yield effective mitragynine doses of ~2 mg/kg (see below), it is expected that maximal plasma concentrations of mitragynine in the low micromolar range may be achievable following consumption of higher doses of kratom plant. Whether this is sufficient to elicit occupancy of central MORs by mitragynine is dependent on brain penetration, which presently remains unknown. Regardless, more rigorous studies in naïve human subjects using pure mitragynine are required to better define the PK parameters and confirm any potential correlation between rodent and human PK. When contrasted with the favorable membrane permeation and metabolic stability of mitragynine found in the *in vitro* assays described above, the apparently low oral bioavailability of this compound is somewhat paradoxical, as it does not seem easily explained by either poor GI absorption or high first-pass metabolism. Further studies are required to reproduce the limited available data and explore the reasons for this low oral bioavailability. Regardless, administration in most animal studies via i. v. or i. p. routes does not reflect the predominant human use as an oral preparation. Differences in bioavailability, metabolism, and interactions with other components in the plant matrix are not sufficiently considered to date.

5.3. Pharmacokinetics of 7-OH

The PK of 7-OH has been examined in one rat study at a single i. v. dose (Vuppala et al., 2013) (see Table 4). This work revealed that 7-OH is more rapidly eliminated ($t_{1/2}$ = 22.9 min) and has a lower V_d than mitragynine. This rapid elimination is consistent with the low stability in liver microsomes (see above). The plasma C_{max} observed was 7.2 μM and thus, given even modest brain

Table 4
Pharmacokinetic parameters of mitragynine and 7-OH.

Compound	Reference	Species/Strain	Dose/Route	Analytical Method	PK parameters in plasma[a]						
					c_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)	V_d[b] (L/kg)	CL[b] (L/(h[a]kg))	AUC ((μg[a]h)/mL)	F
Mitragynine	Janchawee et al., 2007	Wistar Rats	40 mg/kg, p.o.	LC-UV	0.63	1.83	9.43	89.5	~6.3[c]	6.99	~26%[d]
	Valaderes de Moraes et al., 2009	Wistar Rats	20 mg/kg, p.o.	LC-MS/MS	0.424	1.26	3.85	37.9	6.35	3.15	~23%[d]
	Parthasarathy et al., 2010	Sprague-Dawley Rats	50 mg/kg, p.o.	LC-UV	0.70	4.5	6.6	64	7.0	8.2	3.0%
		Sprague-Dawley Rats	1.5 mg/kg, i.v.	LC-UV	2.3	1.2	2.9	0.79	0.29	9.2	
	Vuppala et al., 2011	Sprague-Dawley Rats	5.0 mg/kg, i.v.	LC-MS/MS	3.9	0.017	2.6	8.2	1.2	3.4	–
	Trakulsrichai et al., 2015	Humans	various, oral tea (~0.3 mg/kg[e])	LC-MS	various (~0.105[e])	0.83	23.2	38.0	98.1[f]	various (~0.67[e])	–
7-OH	Vuppala et al., 2013	Sprague-Dawley Rats	4.0 mg/kg, i.v.	LC-MS/MS	3.0	0.033	0.382	1.60	2.65	1.64	–

[a] Data has been converted to uniform units for ease of comparison.
[b] For oral studies, V_d/F and Cl/F.
[c] Estimated post hoc by mean rat bodyweight.
[d] Calculated post hoc using i. v. data from Vuppala et al. (2011).
[e] Representative data for a single subject.
[f] This value appears to be erroneous or lack correct units since it could not possibly yield the observed $t_{1/2}$ given the reported V_d/F.

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penetration, this dose (4 mg/kg i. v.) should be easily sufficient to engage central MORs in the rat. However, doses of 7-OH delivered through kratom consumption are much lower and by the oral route, not i. v. (see below). Therefore, there is insufficient data at present to determine whether the 7-OH dose provided by typical human doses of kratom is centrally active solely based on PK (although analgesic tests suggest that it is not, see below).

6. Observations from human use

6.1. Correlating animal studies with human experiencenotes on dosing and route of administration

Mitragynine and 7-OH do not appear to be available in a pure form to the typical consumer and thus, the potential toxicity and/or abuse liability of such pure compounds is not directly relevant to the risks associated with consumption of the unadulterated plant material or extracts. Likewise, the potential for administration by intravenous or intranasal routes is not currently relevant, given that injection or insufflation of ground plant matter is not reasonably possible. Instead, it is most appropriate to approximate exposure levels to said pure compounds at typical oral dose levels of the raw plant matter (the most common administration route). In a recent survey of 8049 kratom users in the United States, 95% of respondents reported consuming <8 g of raw plant matter per dose (Grundmann, 2017). Thus, based on known mean concentrations of mitragynine and 7-OH in kratom (see above, Table 1), at the upper end of this dose range (8 g), an individual may be exposed to a dose of approximately 120–180 mg of mitragynine and 1.1–3.4 mg of 7-OH (1.7–2.5 mg/kg and 0.015–0.048 mg/kg, respectively, at 70 kg bodyweight).

Utilizing standard dose-scaling allometric ratios based on body surface area (3:6:20:37 = mouse:rat:dog:human), these typical human dose ranges may be converted to corresponding animal dose ranges to allow better correlation of animal data with observations and expectations in man. Thus, an 8-g p. o. dose of kratom plant roughly corresponds to the p. o. animal doses of mitragynine and 7-OH listed in Table 5. It should be noted that this crude analysis is highly preliminary and does not account for differences in PK, which may be significant between species. Thus, further study is needed to better define the PK profile of mitragynine and 7-OH in multiple animal species and man (see above). Nonetheless, the extrapolated dose ranges listed here are useful for preliminary interpretation of animal studies. For example, the p. o. ED_{50} values determined by Macko in rats and dogs are in good agreement (when corrected by allometry) with the expected dose of mitragynine delivered through consumption of an 8-g dose of raw kratom plant. Accordingly, at higher doses reported by human users, kratom is expected to be an efficacious analgesic (as is anecdotally reported) through the opioid actions of mitragynine.

Table 5
Interspecies dosing conversions.

Species	Oral dose range equivalent to 8 g kratom (mg/kg)[a]	
	mitragynine	7-OH
Human	1.7–2.5	0.015–0.048
Dog	3.1–4.6	0.027–0.088
Rat	10–15	0.090–0.29
Mouse	20–30	0.18–0.59

[a] Upper and lower end of dose ranges calculated using combined averages from Table 1 ± 1 standard deviation and assuming a human body mass of 70 kg.

6.1.1. At typical doses of raw kratom plant, exposure to 7-OH is expected to be sub-pharmacological

Opioid-dependent analgesic activity may be considered a reasonable surrogate for opioid receptor occupancy. In most cases, it may also be considered a more sensitive measure than those of euphoria or drug-liking (indicative of abuse liability) considering that most opioid analgesics are used recreationally at doses above those providing effective analgesia (even in naïve individuals). An ED_{50} dose of 2.2 mg/kg p. o., the most potent result for oral analgesic activity in mice, is ~5-fold above the expected 7-OH dose delivered by 8 g of kratom (corrected according to Table 5). Similarly, the minimum dose of 7-OH that elicits motor stimulation and conditioned place preference (CPP) in mice is 2.0 mg/kg s. c. (Matsumoto et al., 2008). When again corrected for route (p.o. at least 2-fold less potent than s. c.) and body size, this suggests a human equivalent dose at least 10-fold greater than the typical exposure from 8 g of kratom (considered a high dose by most users). Accordingly, based on the body of scientific data available at present, it is not clear that 7-OH plays a significant role in the gross behavioral and physiological effects of unadulterated kratom in man at reasonable doses.

6.2. Qualitative behavioral and physiological effects in humans

Unlike animal data, human observations to date are entirely based on observational and case reports. Kratom's main traditional use in Southeast Asia, for stimulant effects at low doses and analgesic effects at high doses, has received both praise and criticism from the research community and general public. The stimulant behavioral effects at single doses of 1–5 g of raw plant material include increased alertness, heightened physical energy, talkativeness, and sociable behavior. A loss of muscle control may occur towards the higher end of this dose range with occasional itching, nausea, loss of appetite, and increased urination being reported as unwanted adverse effects (Swogger et al., 2015; Warner et al., 2016). The effects clearly shift with doses above 8 g, mainly presenting with dizziness, light-headedness, and sedation indicating the opioid-predominant effects, which are accompanied by physiological symptoms of constipation, hypotension, sweating, and dry mouth. Tachycardia is also frequently reported by kratom users consuming 8 g or more of plant material at a time. The intermediate dose range of between 5 and 8 g is least defined and presents with a wide range of effects mixed between those of both higher and lower doses. It appears that the antidepressant and anxiolytic effects of kratom are less dose dependent than the stimulant or analgesic effects and tend to be felt at lower doses of 3–6 g (Table 6)

Table 6
Reported dose-dependent effects of kratom in humans.

Effect	Single kratom dose		
	1-5 g	5-8 g	≥8 g
Stimulant	Increased alertness Talkativeness Physical energy		Tachycardia
Mood-elevating	Anxiolytic Antidepressant Sociable behavior		
Sedative/relaxing	Loss of muscle coordination	Dizziness/unsteadiness	Constipation Hypotension
Adverse effects	Itching Loss of appetite Increased urination		

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(Grundmann, 2017).

The major concern in regard to the unregulated legal status of kratom products is their potential for dependence and abuse based on the effects of the alkaloids mitragynine and 7-OH at opioid receptors. Various publications have reported a high potential for dependence with continued kratom use (Singh et al., 2016, 2014), although the reported withdrawal symptoms are milder compared to those of classical opioids and last 1–3 days (Singh et al., 2014). Likewise, there seems to be a separation between doses inducing the purported therapeutic benefits and higher doses at which physical and/or psychological dependence is more likely to develop (Grundmann, 2017). Furthermore, rapid dose escalation does not appear to be a hallmark of typical kratom use patterns. The possession, planting, export or import of kratom is regulated under the Narcotics Act in Thailand since 1973 because of the growing concern by regulatory agencies of its dependency and abuse potential (Singh et al., 2016). The use of kratom leaves in Thailand, however, has shifted over time with the growth of opium use and misuse/abuse. Kratom was no longer primarily used for its stimulant and analgesic properties, but rather to treat opium abuse, thereby causing a significant number of former opium users to consume kratom to treat withdrawal symptoms. A majority of kratom users, even with increasing chronic use, remain in good health and do not engage in risky drug-seeking or criminal behavior (Singh et al., 2015). The use of kratom, despite its legal status in Thailand, is not seen as a social stigma since most kratom users are older, maintain regular employment, and are married and living with their family. In many cases, they are working hard and use kratom to maintain energy and reduce pain resulting from increasing age.

6.3. Current legal status in the United States, use pattern, and toxic events

The availability of kratom products in the US is not currently regulated at the federal level. The US Food and Drug Administration (FDA) issued a warning in 2014 and has seized a number of kratom-containing shipments and dietary supplements based on consumer safety concerns (Warner et al., 2016). Several US states have placed kratom and the alkaloids mitragynine and 7-OH on the list of controlled substances while the US Drug Enforcement Administration (DEA) has listed it as a "Drug of Concern" as of 2012. In August 2016, the DEA attempted to use emergency authority to place the main alkaloids of kratom (and thereby, also the plant itself) into federal Schedule I (DEA, 2016a) without a prior public comment period and faced significant public backlash, resulting in the withdrawal of such intent in October 2016 (DEA, 2016b). The subsequent public commenting period ended on December 1, 2016 with no further action taken as of June 30, 2017. The reasoning for the intended emergency scheduling by the DEA was based on a report by the Centers for Disease Control and Prevention stating a tenfold increase in calls to poison control centers involving kratom between 2010 and 2015 (Anwar et al., 2016). This relative increase is certainly concerning, although in absolute numbers, the total number of cases (263 in 2015) is less dramatic (Fig. 3). For comparison, in 2014 alone, single acetaminophen exposures resulted in 67,187 calls and 65 reported fatalities (Mowry et al., 2015). Out of the total 660 exposures over the 5-year period, 49 exposures to kratom alone or in combination with other medications/substances were categorized as major and life-threatening with potential residual impairment or disability. One death was reported in a user who also used paroxetine and lamotrigine and therefore, it is not clear that the death can be solely attributed to the use of kratom, and there is also no data on the exposure level in this case (Anwar et al., 2016). The major observed signs and symptoms in these cases align with case reports and earlier observations of kratom users and include tachycardia, drowsiness, irritability, nausea, and hypertension. One reported risk associated with the use of kratom products has been contamination with undeclared *O*-desmethyltramadol, an active and more potent metabolite of the opioid agonist tramadol (Arndt et al., 2011; Scott et al., 2014). Since *O*-desmethyltramadol is not currently regulated as a controlled substance, it has been legally sold in combination with kratom under the brand name "Krypton" (Kronstrand et al., 2011). In nine fatal exposures involving Krypton in Sweden, the whole blood concentrations of mitragynine were 0.02–0.18 μg/g, within the proposed usual range for an oral chronic kratom dose of 5–8 g. In addition, concentrations of *O*-desmethyltramadol ranged from 0.4 to 4.3 μg/g without tramadol or *N*-desmethyltramadol being present, indicating that *O*-desmethyltramadol itself was ingested (Kronstrand et al., 2011). In all nine cases, the deceased had a range of additional drugs in their systems including benzodiazepines, alcohol, antidepressants, or illicit drugs. Given these polyintoxications, it remains unclear what if any role kratom and its alkaloids played in these fatalities. Perhaps most notably, to our knowledge there has been no reported fatal kratom exposure with the classical symptoms of opioid-induced respiratory depression as the cause of death, which suggests that the opioid-like effects of kratom are different from that of classical full opioid agonists.

The use pattern in the US has not been explored systematically to date. Advocacy groups claim that 4–5 million Americans are current users of kratom based on membership alone, but these numbers are likely unreliable. In an anonymous online survey study of kratom users, the subjective qualitative experiences of 161 individuals were analyzed and categorized according to predominantly positive or negative themes such as euphoria and sociability or nausea and dizziness (Swogger et al., 2015). Swogger and colleagues determined that the effects were primarily positive and kratom benefited users in replacing unwanted substances such as opioids and illicit drugs, but that mild symptoms of tolerance and withdrawal effects were also felt. However, the authors caution that the sample was likely biased towards a favorable view of kratom given the small sample size and the retrieval resource from Erowid.org, a recreational-drug-focused website. The results from a large (N = 8049), anonymous US online survey of current kratom users examining demographics, use patterns, adverse and toxic effects, and abuse potential of kratom indicates that the average user is middle-aged (31–50 years), with middle-class income ($35,000 and above), stable employment and health insurance, and primarily uses kratom to treat pain (68%) and emotional or mental conditions (66%) (Grundmann, 2017). A dose-effect relationship was observed for increased energy and focus, less depressed and anxious mood, elevated mood, and decreased use of prescription or illicit opioid drugs, but not for decreased pain. This may indicate that kratom for the most part is effective in relatively low doses without a significant risk for the development of a substance use disorder. In order to understand the impact of kratom use on health and safety in the US population, more epidemiological and clinical research is clearly needed. This is especially important given the ongoing legal situation of kratom in the US, with lawmakers, federal and state regulatory agencies, users, and researchers disagreeing on the legal control of kratom and its major alkaloids. The scientific community has to a large extent voiced concerns that placing kratom, mitragynine, and/or 7-OH in federal Schedule I will impair and prevent needed scientific research that may provide important insights into the harm reduction and medicinal potential of kratom (Pinney Associates, 2016).

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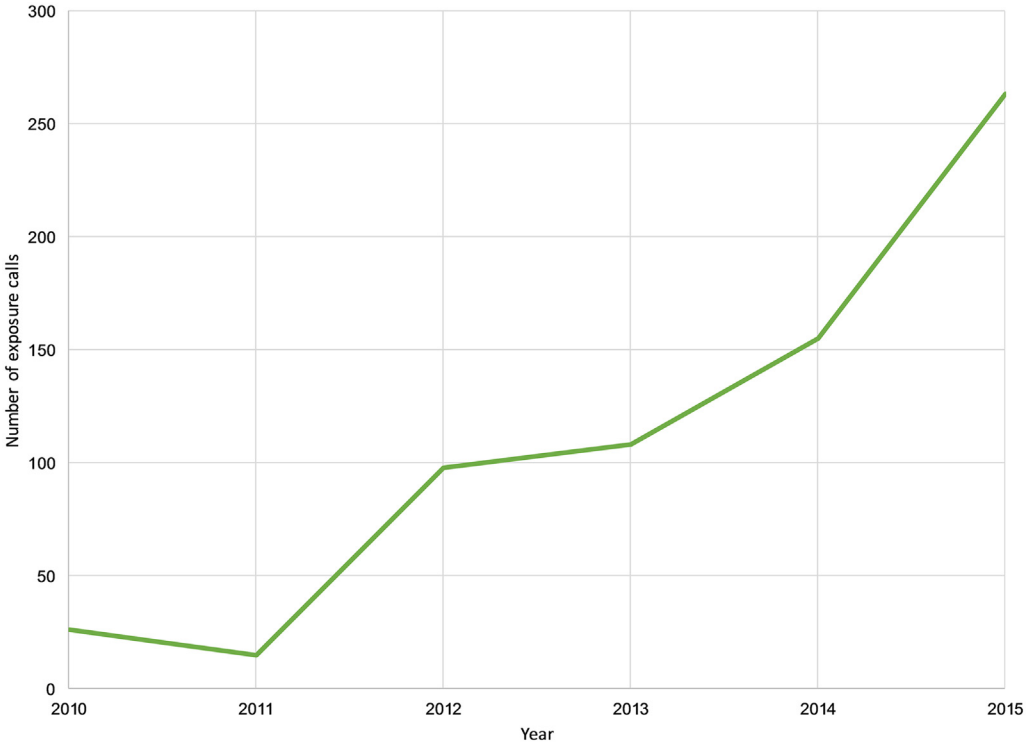

Fig. 3. Number of reported exposure calls to poison centers related to kratom use, by year, United States and Puerto Rico, January 2010–December 2015.

7. Conclusions

Kratom leaf or extracts exert a dose-dependent and complex range of pharmacological effects, some of which can be explained by the opioid activity of the alkaloids mitragynine and 7-OH. Other known but poorly characterized alkaloids or as-yet-unidentified compounds in the plant may also contribute to the observed behavioral effects, particularly the enigmatic stimulant activity. Available *in vitro*, *in vivo*, and observational human data are consistent with opioid agonist activity and a proposed allometric scaling model suggests that analgesic effects require higher doses of extracts or raw plant material. However, *in vitro* studies have shown that mitragynine and 7-OH have mixed agonist-antagonist activity at the opioid receptors and also do not recruit β-arrestin to MOR, which distinguishes them from classical opioids. Likewise, in animals, mitragynine and 7-OH have been shown to induce limited constipation and in the case of mitragynine, less respiratory depression. Thus, these compounds may serve as new molecular scaffolds for the development of centrally acting analgesic drugs with greater therapeutic index. To date, no human fatality can be solely attributed to the ingestion of kratom and reports of adverse effects (e.g. withdrawal symptoms) are typically mild. Likewise, current users appear to be distinctly different in their use pattern and socioeconomic background than typical drug users/abusers.

Based on the known chemistry and pharmacology of kratom, there is a clear knowledge gap in regard to the detailed signaling effects of mitragynine and 7-OH downstream of opioid receptors, the activities of these compounds at non-opioid receptors, the activities of other alkaloids and non-alkaloids in the plant and their potential contributions to the observed pharmacological effects, and pharmacodynamic-pharmacokinetic correlation between *in vitro*, *in vivo*, and human studies. At this point, based only on isolated human observations and without clear knowledge of extent or patterns of use, we can at best hypothesize that the addictive potential of kratom plant or extracts appears lower than that of typical opioid agonists. Likewise, despite a recent increase in kratom-related health incidents, some of them having been reported to be severe or even fatal, no single case can be solely attributed to respiratory failure due to kratom, a sharp contrast to other opioids where respiratory depression is the most common cause of death. Animal studies evaluating tolerance, dependence, and abuse liability have been ambiguous and it would behoove regulatory agencies to first consider ADME processes and common dosing levels and routes before equating unadulterated kratom with potent, full opioid receptor agonists like morphine or heroin. The potential chilling effect of Schedule I control on scientific research should also be considered.

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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.

Anwar, M., Law, R., Schier, J., 2016. Notes from the Field: kratom (*Mitragyna speciosa*) exposures reported to poison centers — United States, 2010–2015. MMWR. Morb. Mortal. Wkly. Rep. 65, 748–749. http://dx.doi.org/10.15585/mmwr.mm6529a4.

Arndt, T., Claussen, U., Güssregen, B., Schröfel, S., Stürzer, B., Werle, A., Wolf, G., 2011. Kratom alkaloids and O-desmethyltramadol in urine of a "Krypton" herbal mixture consumer. Forensic Sci. Int. 208, 47–52. http://dx.doi.org/10.1016/j.forsciint.2010.10.025.

Boyer, E.W., Babu, K.M., Adkins, J.E., McCurdy, C.R., Halpern, J.H., 2008. Self-treatment of opioid withdrawal using kratom (*Mitragyna speciosa* Korth). Addiction 103, 1048–1050. http://dx.doi.org/10.1111/j.1360-0443.2008.02209.x.

Carpenter, J.M., Criddle, C.A., Craig, H.K., Ali, Z., Zhang, Z., Khan, I.A., Sufka, K.J., 2016. Comparative effects of *Mitragyna speciosa* extract, mitragynine, and opioid agonists on thermal nociception in rats. Fitoterapia 109, 87–90. http://dx.doi.org/10.1016/j.fitote.2015.12.001.

de Moraes, N.V., Moretti, R.A.C., Furr, E.B., McCurdy, C.R., Lanchote, V.L., 2009. Determination of mitragynine in rat plasma by LC–MS/MS: application to pharmacokinetics. J. Chromatogr. B 877, 2593–2597. http://dx.doi.org/10.1016/j.jchromb.2009.06.023.

DEA, D.O.J., 2016a. Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine into Schedule I. Federal Register. Document Citation 81 FR 59929. United States Government. https://www.federalregister.gov/documents/2016/08/31/2016-20803/schedules-of-controlled-substances-temporary-placement-of-mitragynine-and-7-hydroxymitragynine-into. (Accessed 30 June 2017).

DEA, D.O.J., 2016b. Withdrawal of Notice of Intent to Temporarily Place Mitragynine and 7-Hydroxymitragynine into Schedule I. Federal Register. Document Citation 81 FR 70652. United States Government. https://www.federalregister.gov/documents/2016/10/13/2016-24659/withdrawal-of-notice-of-intent-to-temporarily-place-mitragynine-and-7-hydroxymitragynine-into. (Accessed 30 June 2017).

FDA, CDER, 2017. Assessment of Abuse Potential of Drugs Guidance for Industry. United States Government. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

Field, E., 1921. XCVIII.—mitragynine and mitraversine, two new alkaloids from species of mitragyne. J. Chem. Soc. Trans. 119, 887–891. http://dx.doi.org/10.1039/CT9211900887.

Grundmann, O., 2017. Patterns of Kratom use and health impact in the US.: results from an online survey. Drug Alcohol Depend. 176, 63–70. http://dx.doi.org/10.1016/j.drugalcdep.2017.03.007.

Hanapi, N.A., Azizi, J., Ismail, S., Mansor, S.M., 2010. Evaluation of selected Malaysian medicinal plants on phase I drug metabolizing enzymes, CYP2C9, CYP2D6 and CYP3A4 activities in vitro. Int. J. Pharmacol. 6, 494–499. http://dx.doi.org/10.3923/ijp.2010.494.499.

Harizal, S.N., Mansor, S.M., Hasnan, J., Tharakan, J.K.J., Abdullah, J., 2010. Acute toxicity study of the standardized methanolic extract of *Mitragyna speciosa* Korth in rodent. J. Ethnopharmacol. 131, 404–409. http://dx.doi.org/10.1016/j.jep.2010.07.013.

Harun, N., Hassan, Z., Navaratnam, V., Mansor, S.M., Shoaib, M., 2015. Discriminative stimulus properties of mitragynine (kratom) in rats. Psychopharmacol. Berl. 232, 2227–2238. http://dx.doi.org/10.1007/s00213-015-3866-5.

Hassan, Z., Muzaimi, M., Navaratnam, V., Yusoff, N.H.M., Suhaimi, F.W., Vadivelu, R., Vicknasingam, B.K., Amato, D., von Hürsten, S., Ismail, N.I.W., Jayabalan, N., Hazim, A.I., Mansor, S.M., Müller, C.P., 2013. From kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. Neurosci. Biobehav. Rev. 37, 138–151. http://dx.doi.org/10.1016/j.neubiorev.2012.11.012.

Hazim, A.I., Ramanathan, S., Parthasarathy, S., Muzaimi, M., Mansor, S.M., 2014. Anxiolytic-like effects of mitragynine in the open-field and elevated plus-maze tests in rats. J. Physiol. Sci. 64, 161–169. http://dx.doi.org/10.1007/s12576-014-0304-0.

Idayu, N.F., Hidayat, M.T., Moklas, M.A.M., Sharida, F., Raudzah, A.R.N., Shamima, A.R., Apryani, E., 2011. Antidepressant-like effect of mitragynine isolated from *Mitragyna speciosa* Korth in mice model of depression. Phytomedicine 18, 402–407. http://dx.doi.org/10.1016/j.phymed.2010.08.011.

Ilmie, M.U., Jaafar, H., Mansor, S.M., Abdullah, J.M., 2015. Subchronic toxicity study of standardized methanolic extract of *Mitragyna speciosa* Korth in Sprague-Dawley Rats. Front. Neurosci. 9, 189. http://dx.doi.org/10.3389/fnins.2015.00189.

Janchawee, B., Keawpradub, N., Chittrakarn, S., Prasettho, S., Wararatananurak, P., Sawangjareon, K., 2007. A high-performance liquid chromatographic method for determination of mitragynine in serum and its application to a pharmacokinetic study in rats. Biomed. Chromatogr. 21, 176–183. http://dx.doi.org/10.1002/bmc.731.

Kerschgens, I.P., Claveau, E., Wanner, M.J., Ingemann, S., van Maarseveen, J.H., Hiemstra, H., Matsumoto, K., Murayama, T., Coccone, S.S., Bernetti, M., De, A.M., Brindisi, M., Nacci, V., Fiorini, I., Novellino, E., Cagnotto, A., Mennini, T., Sandager-Nielsen, K., Andreasen, J.T., Scheel-Kruger, J., Mikkelsen, J.D., Fattorusso, C., 2012. Total syntheses of mitragynine, paynantheine and speciogynine via an enantioselective thiourea-catalysed Pictet–Spengler reaction. Chem. Commun. 48, 12243. http://dx.doi.org/10.1039/c2cc37023a.

Kikura-Hanajiri, R., Kawamura, M., Maruyama, T., Kitajima, M., Takayama, H., Goda, Y., 2009. Simultaneous analysis of mitragynine, 7-hydroxymitragynine, and other alkaloids in the psychotropic plant "kratom" (*Mitragyna speciosa*) by LC-ESI-MS. Forensic Toxicol. 27, 67–74. http://dx.doi.org/10.1007/s11419-009-0070-5.

Kong, W.M., Chik, Z., Ramachandra, M., Subramaniam, U., Aziddin, R.E.R., Mohamed, Z., 2011. Evaluation of the effects of *Mitragyna speciosa* alkaloid extract on cytochrome P450 enzymes using a high throughput assay. Molecules 16, 7344–7356. http://dx.doi.org/10.3390/molecules16097344.

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, 242–247.

Kruegel, A.C., Gassaway, M.M., Kapoor, A., Váradi, A., Majumdar, S., Filizola, M., Javitch, J.A., Sames, D., 2016. Synthetic and receptor Signaling explorations of the *Mitragyna* alkaloids: Mitragynine as an atypical Molecular framework for opioid receptor Modulators. J. Am. Chem. Soc. 138, 6754–6764. http://dx.doi.org/10.1021/jacs.6b00360.

Kumarnsit, E., Vongvatcharanon, U., Keawpradub, N., Intasaro, P., 2007. Fos-like immunoreactivity in rat dorsal raphe nuclei induced by alkaloid extract of *Mitragyna speciosa*. Neurosci. Lett. 416, 128–132. http://dx.doi.org/10.1016/j.neulet.2007.01.061.

León, F., Habib, E., Adkins, J.E., Furr, E.B., McCurdy, C.R., Cutler, S.J., 2009. Phytochemical characterization of the leaves of *Mitragyna speciosa* grown in U.S.A. Nat. Prod. Commun. 4, 907–910.

Lydecker, A.G., Sharma, A., McCurdy, C.R., Avery, B.A., Babu, K.M., Boyer, E.W., 2016. Suspected adulteration of commercial kratom products with 7-hydroxymitragynine. J. Med. Toxicol. 12, 341–349. http://dx.doi.org/10.1007/s13181-016-0588-y.

Ma, Jun, Yin, Wenyuan, Zhou, Hao, Cook, J.M., 2007. Total synthesis of the opioid agonistic indole alkaloid mitragynine and the first total syntheses of 9-methoxygeissoschizol and 9-methoxy-nb-methylgeissoschizol. Org. Lett. 30, 3491–3494. http://dx.doi.org/10.1021/OL071220L.

Ma, J., Yin, W., Zhou, H., Liao, X., Cook, J.M., 2009. General approach to the total Synthesis of 9-Methoxy-substituted indole alkaloids: Synthesis of Mitragynine, as well as 9-Methoxygeissoschizol and 9-Methoxy- *N* b -methylgeissoschizol. J. Org. Chem. 74, 264–273. http://dx.doi.org/10.1021/jo801839t.

Macko, E., Weisbach, J.A., Douglas, B., 1972. Some observations on the pharmacology of mitragynine. Arch. Int. Pharmacodyn. thérapie 198, 145–161.

Manda, V., Avula, B., Ali, Z., Khan, I., Walker, L., Khan, S., 2014. Evaluation of in vitro absorption, distribution, metabolism, and excretion (ADME) properties of Mitragynine, 7-hydroxymitragynine, and Mitraphylline. Planta Med. 80, 568–576. http://dx.doi.org/10.1055/s-0034-1368444.

Matsumoto, K., 2006. Pharmacological Studies on 7-Hydroxymitragynine, Isolated from the Thai Herbal Medicine *Mitragyna speciosa*: Discovery of an Orally Active Opioid Analgesic (Ph.D. Dissertation). Chiba University, Chiba, Japan.

Matsumoto, K., Mizowaki, M., Suchitra, T., Murakami, Y., Takayama, H., Sakai, S., Aimi, N., Watanabe, H., 1996a. Central antinociceptive effects of mitragynine in mice: contribution of descending noradrenergic and serotonergic systems. Eur. J. Pharmacol. 317, 75–81. http://dx.doi.org/10.1016/S0014-2999(96)00714-5.

Matsumoto, K., Mizowaki, M., Suchitra, T., Takayama, H., Sakai, S., Aimi, N., Watanabe, H., 1996b. Antinociceptive action of mitragynine in mice: evidence for the involvement of supraspinal opioid receptors. Life Sci. 59, 1149–1155.

Matsumoto, K., Horie, S., Ishikawa, H., Takayama, H., Aimi, N., Ponglux, D., Watanabe, K., 2004. Antinociceptive effect of 7-hydroxymitragynine in mice: discovery of an orally active opioid analgesic from the Thai medicinal herb *Mitragyna speciosa*. Life Sci. 74, 2143–2155. http://dx.doi.org/10.1016/j.lfs.2003.09.054.

Matsumoto, K., Horie, S., Takayama, H., Ishikawa, H., Aimi, N., Ponglux, D., Murayama, T., Watanabe, K., 2005. Antinociception, tolerance and withdrawal symptoms induced by 7-hydroxymitragynine, an alkaloid from the Thai medicinal herb *Mitragyna speciosa*. Life Sci. 78, 2–7. http://dx.doi.org/10.1016/j.lfs.2004.10.086.

Matsumoto, K., Takayama, H., Narita, M., Nakamura, A., Suzuki, M., Suzuki, T., Murayama, T., Wongseripipatana, S., Misawa, K., Kitajima, M., Tashima, K., Horie, S., 2008. MGM-9 [(E)-methyl 2-(3-ethyl-7a,12a-(epoxyethanoxy)-9-fluoro-1,2,3,4,6,7,12,12b-octahydro-8-methoxyindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate], a derivative of the indole alkaloid mitragynine: a novel dual-acting mu- and kappa-opioid agonist with pot. Neuropharmacology 55, 154–165. http://dx.doi.org/10.1016/j.neuropharm.2008.05.003.

Mohamad, A.M.M., Noor, A.S., Che, N.M.T., Hidayat, B.M.T., 2013. Sedative, cognitive impairment and anxiolytic effects of acute *Mitragyna Speciosa* in rodents. J. US-China Med. Sci. 10 http://dx.doi.org/10.17265/1548-6648/2013.01.005.

Mowry, J.B., Spyker, D.A., Brooks, D.E., McMillan, N., Schauben, J.L., 2015. 2014 annual report of the american association of poison control centers' National poison data System (NPDS): 32nd annual report. Clin. Toxicol. 53, 962–1147. http://dx.doi.org/10.3109/15563650.2015.1102927.

Parthasarathy, S., Ramanathan, S., Ismail, S., Adenan, M.I., Mansor, S.M., Murugaiyah, V., 2010. Determination of mitragynine in plasma with solid-phase extraction and rapid HPLC–UV analysis, and its application to a pharmacokinetic study in rat. Anal. Bioanal. Chem. 397, 2023–2030. http://dx.doi.org/10.1007/s00216-010-3707-7.

Paul, D., Pick, C.G., Tive, L.A., Pasternak, G.W., 1991. Pharmacological characterization of nalorphine, a kappa 3 analgesic. J. Pharmacol. Exp. Ther. 257, 1–7.

Pinney Associates, 2016. Assessment of Kratom under the CSA Eight Factors and Scheduling Recommendation. http://216.30.191.148/HL-AKA-Eight_Factor_and_Recommendations_by_PinneyAssoc.pdf. (Accessed 30 June 2017).

Ponglux, D., Wongseripipatana, S., Takayama, H., Kikuchi, M., Kurihara, M., Kitajima, M., Aimi, N., Sakai, S., 1994. A new indole alkaloid, 7 alpha-Hydroxy-7H-mitragynine, from *Mitragyna speciosa* in Thailand. Planta Med. 60, 580–581. http://dx.doi.org/10.1055/s-2006-959578.

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, 792–799.

Raffa, R.B., Beckett, J.R., Brahmbhatt, V.N., Ebinger, T.M., Fabian, C.A., Nixon, J.R., Orlando, S.T., Rana, C.A., Tejani, A.H., Tomazic, R.J., 2013. Orally active opioid compounds from a non-poppy source. J. Med. Chem. 56, 4840–4848. http://dx.doi.org/10.1021/jm400143z.

Reanmongkol, W., Keawpradub, N., Sawangjaroen, K., 2007. Effects of the extracts from *Mitragyna speciosa* Korth. leaves on analgesic and behavioral activities in experimental animals. Songklanakarin J. Sci. Technol. 29, 39–48.

Sabetghadam, A., Ramanathan, S., Mansor, S.M., 2010. The evaluation of anti-nociceptive activity of alkaloid, methanolic, and aqueous extracts of Malaysian *Mitragyna speciosa* Korth leaves in rats. Pharmacogn. Res. 2, 181–185. http://dx.doi.org/10.4103/0974-8490.65514.

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Sabetghadam, A., Navaratnam, V., Mansor, S.M., 2013a. Dose-response relationship, acute toxicity, and therapeutic index between the alkaloid extract of *Mitragyna speciosa* and its Main active compound Mitragynine in Mice. Drug Dev. Res. 74, 23–30. http://dx.doi.org/10.1002/ddr.21052.

Sabetghadam, A., Ramanathan, S., Sasidharan, S., Mansor, S.M., 2013b. Subchronic exposure to mitragynine, the principal alkaloid of *Mitragyna speciosa*, in rats. J. Ethnopharmacol. 146, 815–823. http://dx.doi.org/10.1016/j.jep.2013.02.008.

Scott, T.M., Yeakel, J.K., Logan, B.K., 2014. Identification of mitragynine and *O*-desmethyltramadol in Kratom and legal high products sold online. Drug Test. Anal. 6, 959–963. http://dx.doi.org/10.1002/dta.1673.

Shaik Mossadeq, W.M., Sulaiman, M.R., Tengku Mohamad, T.A., Chiong, H.S., Zakaria, Z.A., Jabit, M.L., Baharuldin, M.T.H., Israf, D.A., 2009. Anti-inflammatory and antinociceptive effects of *Mitragyna speciosa* Korth. Methanolic extract. Med. Princ. Pract. 18, 378–384. http://dx.doi.org/10.1159/000226292.

Shellard, E.J., 1974. The alkaloids of Mitragyna with special reference to those of *Mitragyna speciosa*. Korth. Bull. Narc. 26, 41–55.

Singh, D., Müller, C.P., Vicknasingam, B.K., 2014. Kratom (*Mitragyna speciosa*) dependence, withdrawal symptoms and craving in regular users. Drug Alcohol Depend. 139, 132–137. http://dx.doi.org/10.1016/j.drugalcdep.2014.03.017.

Singh, D., Müller, C.P., Vicknasingam, B.K., Mansor, S.M., 2015. Social functioning of kratom *(Mitragyna speciosa)* users in Malaysia. J. Psychoact. Drugs 47, 125–131. http://dx.doi.org/10.1080/02791072.2015.1012610.

Singh, D., Narayanan, S., Vicknasingam, B., 2016. Traditional and non-traditional uses of Mitragynine (Kratom): a survey of the literature. Brain Res. Bull. 126, 41–46. http://dx.doi.org/10.1016/j.brainresbull.2016.05.004.

Siuda, E.R., Carr, R., Rominger, D.H., Violin, J.D., 2017. Biased mu-opioid receptor ligands: a promising new generation of pain therapeutics. Curr. Opin. Pharmacol. 32, 77–84. http://dx.doi.org/10.1016/j.coph.2016.11.007.

Sufka, K.J., Loria, M.J., Lewellyn, K., Zjawiony, J.K., Ali, Z., Abe, N., Khan, I.A., 2014. The effect of *Salvia divinorum* and *Mitragyna speciosa* extracts, fraction and major constituents on place aversion and place preference in rats. J. Ethnopharmacol. 151, 361–364. http://dx.doi.org/10.1016/j.jep.2013.10.059.

Suhaimi, F.W., Yusoff, N.H.M., Hassan, R., Mansor, S.M., Navaratnam, V., Müller, C.P., Hassan, Z., 2016. Neurobiology of Kratom and its main alkaloid mitragynine. Brain Res. Bull. 126, 29–40. http://dx.doi.org/10.1016/j.brainresbull.2016.03.015.

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, 360–367. http://dx.doi.org/10.1080/02791072.2015.1096434.

Takayama, H., 2004. Chemistry and pharmacology of analgesic indole alkaloids from the Rubiaceous plant, Mitragyna Speciosa. Chem. Pharm. Bull. (Tokyo) 52, 916–928. http://dx.doi.org/10.1248/cpb.52.916.

Takayama, H., Maeda, M., Ohbayashi, S., Kitajima, M., Sakai, S., Aimi, N., 1995. The first total synthesis of (−)-mitragynine, an analgesic indole alkaloid in mitragyna speciosa. Tetrahedron Lett. 36, 9337–9340. http://dx.doi.org/10.1016/0040-4039(95)02022-H.

Takayama, H., Ishikawa, H., Kurihara, M., Kitajima, M., Aimi, N., Ponglux, D., Koyama, F., Matsumoto, K., Moriyama, T., Yamamoto, L.T., Watanabe, K., Murayama, T., Horie, S., 2002. Studies on the Synthesis and opioid agonistic activities of Mitragynine-related indole alkaloids: discovery of opioid agonists Structurally different from other opioid ligands. J. Med. Chem. 45, 1949–1956. http://dx.doi.org/10.1021/jm010576e.

Tohda, M., Thongpraditchote, S., Matsumoto, K., Murakami, Y., Sakai, S., Aimi, N., Takayama, H., Tongroach, P., Watanabe, H., 1997. Effects of mitragynine on cAMP formation mediated by delta-opiate receptors in NG108-15 cells. Biol. Pharm. Bull. 20, 338–340.

Trakulsrichai, S., Sathirakul, K., Auparakkitanon, S., Krongvorakul, J., Sueajai, J., Noumjad, N., Sukasem, C., Wananukul, W., 2015. Pharmacokinetics of mitragynine in man. Drug Des. devel. Ther. 9, 2421–2429. http://dx.doi.org/10.2147/DDDT.S79658.

Váradi, A., Marrone, G.F., Palmer, T.C., Narayan, A., Szabó, M.R., Le Rouzic, V., Grinnell, S.G., Subrath, J.J., Warner, E., Kalra, S., Hunkele, A., Pagirsky, J., Eans, S.O., Medina, J.M., Xu, J., Pan, Y.-X., Borics, A., Pasternak, G.W., McLaughlin, J.P., Majumdar, S., 2016. Mitragynine/corynantheidine Pseudoindoxyls as opioid analgesics with Mu agonism and delta antagonism, which do not recruit β-arrestin-2. J. Med. Chem. 59, 8381–8397. http://dx.doi.org/10.1021/acs.jmedchem.6b00748.

Vuppala, P.K., Boddu, S.P., Furr, E.B., McCurdy, C.R., Avery, B.A., 2011. Simple, Sensitive, high-throughput Method for the quantification of Mitragynine in rat plasma using UPLC-MS and its application to an intravenous pharmacokinetic Study. Chromatographia 74, 703–710. http://dx.doi.org/10.1007/s10337-011-2128-x.

Vuppala, P.K., Jamalapuram, S., Furr, E.B., McCurdy, C.R., Avery, B.A., 2013. Development and validation of a UPLC-MS/MS method for the determination of 7-hydroxymitragynine, a μ-opioid agonist, in rat plasma and its application to a pharmacokinetic study. Biomed. Chromatogr. 27, 1726–1732. https://doi.org/10.1002/bmc.2986.

Warner, M.L., Kaufman, N.C., Grundmann, O., 2016. The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. Int. J. Leg. Med. 130, 127–138. http://dx.doi.org/10.1007/s00414-015-1279-y.

Yusoff, N.H.M., Suhaimi, F.W., Vadivelu, R.K., Hassan, Z., Rümler, A., Rotter, A., Amato, D., Dringenberg, H.C., Mansor, S.M., Navaratnam, V., Müller, C.P., 2016. Abuse potential and adverse cognitive effects of mitragynine (kratom). Addict. Biol. 21, 98–110. http://dx.doi.org/10.1111/adb.12185.

Yusoff, N.H.M., Mansor, S.M., Müller, C.P., Hassan, Z., 2017. Opioid receptors mediate the acquisition, but not the expression of mitragynine-induced conditioned place preference in rats. Behav. Brain Res. 332, 1–6. http://dx.doi.org/10.1016/j.bbr.2017.05.059.

Zacharias, D.E., Rosenstein, R.D., Jeffrey, G.A., 1965. The structure of mitragynine hydroiodide. Acta Crystallogr. 18, 1039–1043. http://dx.doi.org/10.1107/S0365110X65002499.

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