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Pharmacokinetics of mitragynine, a major analgesic alkaloid in kratom (*Mitragyna speciosa*): A systematic review

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ABSTRACT

Background and objective: Kratom (*Mitragyna speciosa*) is a tropical tree found in southern Thailand and northern states of the Malay Peninsula. Kratom is commercially available and used as an alternative to treat opioid withdrawal. Mitragynine is the major indole alkaloid found in kratom leaves. This review aimed to summarize available pharmacokinetic information about mitragynine.

Methods: PubMed, Scopus, and Web of Science were systematically searched from their inceptions to June 2018. All types of pharmacokinetic studies of mitragynine were included for further systematic review.

Results: Seventeen articles were reviewed. Mitragynine is a lipophilic weak base passively transported across the intestinal wall and blood brain barrier. 85–95% is bound to plasma protein and extensively metabolized by phase I and particularly phase II enzymes. Actions on CYP enzymes are unlikely to impact drug metabolism at concentrations likely to exist in kratom-consuming humans. In rats and humans, mitragynine is rapidly absorbed after orally administration (T_{max}~1.5 h, C_{max}~0.3 − 1.8 μM). V_d was 37–90 L/kg; $t_{1/2}$ was 3–9 hr; mostly excreted as metabolites in urine. Bioavailability was estimated as 21%. It also rapidly penetrated and redistributed in brain. A quality assessment tool tailored for pharmacokinetic studies was also created which rated some studies of lower value.

Conclusion: Rudimentary pharmacokinetics of mitragynine was described in this systematic review. However, the discovered studies provided scant information on the role of metabolism and redistribution into tissues nor the rate of excretion.

1. Introduction

Mitragyna speciosa (Rubiaceae) is a tropical tree common in southern Thailand and the adjoining northern Malaysia. In Thailand, it is variously known as kratom, thom, ithang, kakuam, kraton, krathom, and as biak-biak, ketum in Malaysia (Hassan et al., 2013; Tanguay, 2011; Warner et al., 2016). Traditionally, kratom is consumed by chewing the fresh leaves, smoking dried leaves, or as tea from dried leaves (Tanguay, 2011). In Southeast Asia, laborers eat its fresh leaves to promote physical endurance, to increase energy, to relief fatigue, and to improve their heat tolerance. Kratom also has appeared in folk remedy to treat some illnesses including coughing, diarrhea, diabetes, and hypertension (Assanangkornchai et al., 2007). Kratom leaves showed opioid-like effect in dose-dependent (Prozialeck et al., 2012). Kratom has many adverse effects including anorexia, dehydration, weight loss, hyperpigmentation (green/dark colored skin), constipation, and psychosis (Saingam et al., 2013; Vicknasingam et al., 2010). However, kratom is rapidly becoming a substance of abuse in southern Thailand; it is consumed as homemade ice-cocktails called a "4 × 100 Cocktail" where kratom leaves are suspended "Coca-Cola" with codeine or diphenhydramine syrup (Tanguay, 2011; White, 2018). Kratom is also consumed as a herbal blend called "krypton" which is a mixture of

Abbreviations: Caco-2, human colonic adenocarcinoma; MDR-MDCK, Multidrug Resistance Protein in Madin-Darby Canine Kidney; CYP, cytochrome P450; P-gp, P-glycoprotein; C_{max}, maximum serum/plasma concentration; T_{max}, time to reach maximum concentration; $t_{1/2}$, half-life; AUC, area under the curve; F, oral bioavailability; V_d, volume distribution; CL, clearance

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kratom leaves with O-desmethyltramadol and sold widely on the internet (Arndt et al., 2011). Regarding to uncertainly on safety and efficacy, kratom is monitored as controlled substance in some countries. Kratom is classified as a narcotic and illegal in some countries including Malaysia, Myanmar, and Australia (Singh et al., 2016) but currently Thai National Legislation Assembly permits kratom for medical use only (Narcotics Act No.7 B.E. (2562) (2019)). Currently, it is not controlled but under surveillance in the UK and Germany and the US where stocks are confiscated by the US Food and Drug Administration (Hassan et al., 2013; Prozialeck et al., 2012; Schmidt et al., 2011). It is commercially available as a dietary supplement for chronic pain (Boyer et al., 2007), and as an alternative treatment for opioid withdrawal (Boyer et al., 2008). Although, kratom is considered as not an illegal substance in most states in the US. However, an increasingly trend of kratom use as well as its adverse events was observed (Galbis-Reig, 2016). Kratom toxicity and the potential associated fatalities have been reported when kratom is used concurrently with other substances, i.e. propylhexedrine (Holler et al., 2011), O-desmethyltramadol (Kronstrand et al., 2011). Kratom also has a psychoactive effect as opioid substance lead to physically dependent or addiction. Thus, kratom is increasingly emerged as an abuse potential in the western countries (Singh et al., 2014). Nonetheless, with its effects to the central nervous system, mitragynine can have additive effects. Therefore, its use of this psychoactive alkaloid should be controlled.

More than 40 alkaloids have been isolated from kratom (Adkins et al., 2011). Among these, mitragynine is the principle indole alkaloid in Thai kratom (66% of total alkaloids) when extracted by organic solvents (Adkins et al., 2011; Ponglux et al., 1994). Mitragynine shares many kratom effects including its opioid action (Prozialeck et al., 2012; Warner et al., 2016). In addition, mitragynine has antinociceptive/analgesic, ileal relaxing and gastric relaxing effects (Suhaimi et al., 2016). It also appears to be an antidepressant (Idayu et al., 2011), and an anti-inflammatory (Utar et al., 2011). The molecular targets of mitragynine are μ opioid receptors acting as a partial agonist while being a competitive antagonist at κ and δ opioid receptors. Full agonists such as morphine, recruit β-arrestin of the μ receptor which mediates much of the opiate toxicity, particularly respiratory depression. β-arrestin also inhibits the G-protein signaling which is normally responsible for analgesia but leads to opiate tolerance (Camilleri, 2018). In contrast, mitragynine is a G-protein-biased agonist at μ opioid receptors but without recruiting β-arrestin, thus causing less respiratory depression while maintaining analgesia (Kruegel et al., 2016). There is increasing interest in partial agonist of μ opioid receptors including mitragynine as alternatives to opiates. In addition, mitragynine also bind to alpha-2 adrenergic receptor, adenosine, dopamine D2 receptors and serotonin receptors but the affinity between mitragynine and these receptors has not well-described.

In some countries, over-prescribing of opiate analgesic can lead to addiction. Kratom has been used as an alternative for opiate addiction (Boyer et al., 2008). Thus, the legalization of kratom in Thailand paves the way to the development of safer analgesic medications. A necessary prelude to this is having the ability to predict mitragynine disposition on overall efficacy. Mitragynine has the potential as a replacement for opiate analgesics but its therapeutic window or controlled clinical trials on the safety and efficacy needs better defining which needs clear understanding its pharmacokinetics. To this end, we aimed to systematically review the pharmacokinetics and relevant properties of mitragynine from the available scientific literature.

2. Methods

2.1. Data sources and search strategy

Studies related to pharmacokinetics of mitragynine were systematically searched from three databases: PubMed, Scopus, and Web of Science from their inception to June 2018. The search terms were kratom OR ketum OR “biak-biak” OR kakuam OR ithang OR thom OR krathom OR kraton OR mitragynine OR "Mitragyna speciosa".

2.2. Study selection

Two reviewers (KY and WT) independently appraised titles and abstracts retrieved from the searches. Any disputes were resolved by a third reviewer (ML). Studies were included if they met all of the following criteria: (1) studies investigating pharmacokinetics of mitragynine or pharmacokinetic-related properties of mitragynine (i.e. solubility, permeability) through *in vitro*, *in situ*, *in vivo* either with experimental animals or human participants; and (2) studies providing sufficient information on the pharmacokinetics of mitragynine including methodology and routes of administration. The exclusion criteria were the following: (1) not written in English; (2) review articles, surveys, case reports, policies; (3) pharmacological effects and toxicities; and (4) pharmacokinetic studies on non-mitragynine alkaloids. Bibliographies of the included articles were examined to identify additional studies. If sufficient details were provided, abstracts and non-journal publications were included. All procedures of the study selection were performed using the PRISMA statement (Moher et al., 2009).

2.3. Data extraction

Data extraction from all the selected articles were performed by two reviewers (KY and WT) and discrepancies were resolved through discussion with a third reviewer (ML). The following data were extracted from studies: (1) physicochemical properties, solubility, and permeability; (2) plasma protein binding; (3) metabolism and membrane transport; and (4) pharmacokinetic parameters in animals and humans.

2.4. Quality assessment

An essential part of a PRISMA systematic review is a quality assessment of extracted studies but often confined to clinical studies focusing on risk of bias tools. Increasingly, tools reflecting CONSORT and ARRIVE are being used to provide more comprehensive quality assessment in animal and clinical studies (Gagnier et al., 2006; Kilkenny et al., 2010). The CONSORT (consolidated standards of reporting trials) statement for randomized controlled clinical trials is applied to control for bias in clinical intervention including herbal products (Gagnier et al., 2006). The ARRIVE (animals in research: reporting *in vivo* experiments) is a guideline that help to improve reporting of research using animals (Kilkenny et al., 2010). Therefore, we adapted CONSORT and ARRIVE checklist items into a quality assessment tool equally applicable for animal and human pharmacokinetic studies (Table 4). The guidance notes for users is given in supplement S1. Only 6 pharmacokinetic studies underwent this assessment (de Moraes et al., 2009; Janchawee et al., 2007; Kong et al., 2017b; Parthasarathy et al., 2010; Trakulsrichai et al., 2015; Vuppala et al., 2011).

3. Results

3.1. Study selection

Of the 7348 articles identified from the databases, title and abstract screening left 419 studies that fitted the eligibility criteria. Exclusion criteria removed 402 of these leaving 17 studies for this systematical review as shown in the PRISMA flow diagram (Fig. 1).

3.2. Study characteristic

Among these 17 selected articles, 9 studies were performed *in vitro* to test mitragynine solubility, permeability to lipid bilayers or cell monolayers, plasma protein binding, metabolic stability, and disposition of mitragynine (metabolism and/or transport) (Anwar et al., 2012;

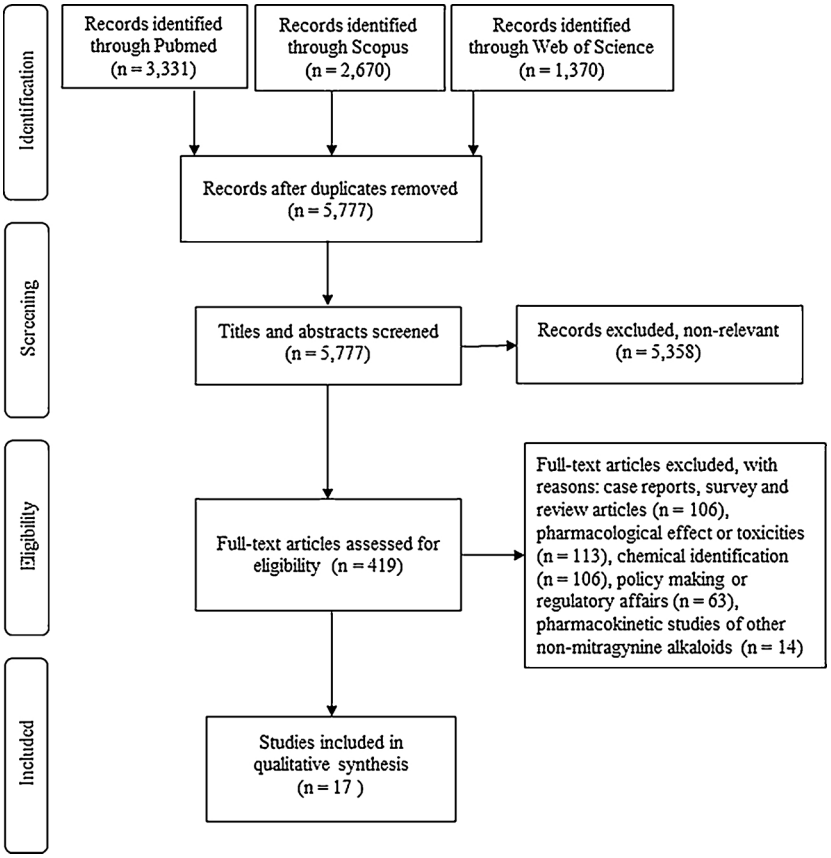

Fig. 1. PRISMA flow diagram of this study 21.

Hanapi et al., 2013; Haron and Ismail, 2015; Kong et al., 2017a; Lim et al., 2013; Manda et al., 2014, 2017; Meyer et al., 2015; Ramanathan et al., 2015). One study used intestine *in situ* to measure mitragynine permeability to the intact intestinal wall (Jagabalan et al., 2018). There were 6 *in vivo* studies: 1 study identified mitragynine metabolites in rats and in humans urine; 5 studies administered mitragynine intravenously or orally to rats and blood sampled for pharmacokinetic studies (de Moraes et al., 2009; Janchawee et al., 2007; Kong et al., 2017b; Parthasarathy et al., 2010; Philipp et al., 2009; Vuppala et al., 2011). One study determined mitragynine pharmacokinetics in humans (Trakulsrichai et al., 2015)

3.3. Physicochemical properties of mitragynine

Mitragynine is an indole alkaloid (Fig. 2) comprising 66% of total alkaloids in extracts of *Mitragyna speciosa* leaves (Adkins et al., 2011; Ponglux et al., 1994). Mitragynine is a weak base (pKa = 8.1) and lipophilic (Log P = 1.73) (Ramanathan et al., 2015). In an aqueous media at pH 4 and 7, mitragynine would be dissolved with concentration levels of 130 μM and 83 μM, respectively (Kong et al., 2017a). This compound at 37 °C was moderately stable at neural pH (~3.5% degradation after 3 h) but degraded at pH 1.2 (by 26% degradation after 1–2 hr) (Manda et al., 2014; Ramanathan et al., 2015), Table 1(a).

3.4. Pharmacokinetics of mitragynine

3.4.1. Absorption

Absorption in vitro: mitragynine fluxes through the phospholipid bilayer at pH 4 and 7.4 were 0.23×10^{-6} and 11×10^{-6} cm/s, respectively (Kong et al., 2017a); these values suggested that mitragynine permeated as the unionized form. In coherent Caco-2 cell monolayers

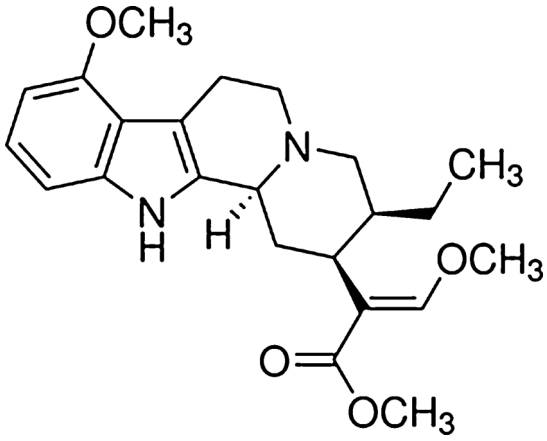

Fig. 2. Chemical structure of mitragynine 21.

(imitating the intestinal barrier), forward and reverse fluxes were 25×10^{-6} and 27×10^{-6} cm/s, which were independent of concentration (Manda et al., 2014). Flux ratios of mitragynine were approximately equated 1, as indicated passively diffusion through membranes. Those results suggested that mitragynine is not a substrate for P-glycoprotein (P-gp). Interestingly, mitraphylline, a minor kratom constituent, was strongly extruded by P-gp. Likewise, mitragynine fluxes across MDR-MDCK cell monlayers (model of the blood brain barrier) were symetrical 15×10^{-6} and 17×10^{-6} cm/s, respectively (Manda et al., 2014). Mitragynine was rated as diffusible using atenolol, propranolol, caffeine, carbamazepine, furosemide, and metoprolol as comparators, as summarized in Table 1(b).

Absorption across the gut epithelium: another study measured mitragynine permeability to intact intestine *in situ* as 1.11×10^{-4} cm/s in

Table 1
In vitro experiment responsible on solubility and permeability of mitragynine.

(a): solubility determinations

Media (incubation period)	pH	Solubility (μM) (% RD)	Reference
SGF (120 min)	1.2	8.03 ± 0.5 (26%)	(Manda et al., 2014)
SIF (180 min)	6.8	10.79 ± 0.25 (3.6%)	
SGF (60 min)	1.2	35.13 ± 0.5 (26%)	(Ramanathan et al., 2015)
SIF (180 min)	6.8	17.57 ± 2.01 (3.5%)	
Water	4	130.0 ± 0.1[a]	(Kong et al., 2017a)
	7	82.7 ± 1.9[b]	

(b): apparent permeability (P_{app} = 10^{-6} cm/s) through cell layers Caco-2 colonic epithelial, brain vascular endothelial cell, and artificial membranes

Model	Compound (tested concentration)	P_{app} (10^{-6} cm/sec)		Reference
		Absorptive flux	Secretory flux	
Gut wall Caco-2 cell monolayers	Mitragynine (5 μM)	24.2 ± 2.6	26.3 ± 2.7	(Manda et al., 2014)
	Mitragynine (10μM)	25.3 ± 2.2	29.1 ± 2.0	
	Atenolol (200μM)	2.0 ± 0.6	2.1 ± 0.4	
	Propranolol (200μM)	34.2 ± 2.6	35.4 ± 1.9	
Brain endothelial MDR-MDCK cells monolayer	Mitragynine (5 μM)	15.3 ± 1.7	17.2 ± 1.6	
	Mitragynine (10μM)	16.2 ± 1.8	18.1 ± 1.7	
	Atenolol (200μM)	1.1 ± 0.2	1.2 ± 0.1	
	Caffeine (100μM)	23.2 ± 2.8	24.3 ± 1.5	
PAMPA	Mitragynine	0.23 ± 0.0005	11.14 ± 0.06	(Kong et al., 2017a)
	Carbamazepine	0.21 ± 0.005	0.13 ± 0.002	
	Furosemide	0.72 ± 0.008	0.75 ± 0.003	
	Metoprolol	4.55 ± 0.002	4.49 ± 0.007	

Abbreviations:SGF = simulated gastric fluid; SIF = simulated intestinal fluid; RD = relative deviation; DES = diethylstilbestrol; Caco-2 cells = human colonic adenocarcinoma cells; MDR-MDCK = multi drug resistance in Madin-Darby Canine Kidney; PAMPA = parallel artificial membrane permeability assay; P_{app} = apparent permeability.
DES (24.1 ± 4.2 μM), estriol (89.8 ± 8.17 μM), and furosemide (187.8 ± 1.0 μM), respectively.
DES (19.3 ± 0.5 μM), estriol (86.5 ± 3.0 μM), and furosemide (197.5 ± 3.1μM), respectively.
[a]At pH 4, this value was compared to low, medium, and high solubility references as followed.
[b]At pH 7, this value was compared to low, medium, and high solubility references as followed.

the absorption direction (Jagabalan et al., 2018), which compared favourably with permeant propranolol (1.12×10^{-4} cm/s) and atenolol (0.41×10^{-4} cm/s). The inhibitors of P-gp (azithromycin) or CYP3A4 (cirprofloxacin) had no influence on mitragynine fluxes (1.13×10^{-4} cm/s and 1.17×10^{-4} cm/s), again suggesting that mitragynine absorption is passive and rapid.

3.4.2. Binding to plasma protein

By equilibrium dialysis, about 95% of mitragynine at tested concentration range of 5–15 μM bound to plasma protein after 24 h at 37 °C in human plasma (Manda et al., 2014). About 85% of mitragynine at a tested concentration of 10 μM binds to plasma proteins after 1 h at 37 °C in human plasma, determined by ultrafiltration (Kong et al., 2017a).

3.4.3. Metabolism and excretion

For metabolism of mitragynine, most of its metabolism occurs in the liver. Both phase I and phase II metabolism involved in the metabolism of this psychoactive alkaloid. There were several studies investigating roles of phase I and phase II using a system with liver microsomes or liver S9 fratcitons (Kong et al., 2017a; Manda et al., 2014), as summarized in Table 2(a). Interestingly, Philipp et al. (2009) measured urinary metabolites by LC–MS/MS after oral dosing of 40 mg/kg mitragynine to rats and urine samples were collected after 24 h. Seven phase I mitragynine metabolites were identified and a further 5 conjugates as one sulphonate and 4 glucuronides presumed to be phase II metabolites. In human urine, 3 sulphonates and 4 glucuronidates were found (Philipp et al., 2009). Mitragynine metabolites were summarized in Table 2(b). Numerous other metabolites were found in urine samples referred for toxicology assessment but had no accompanying history. Samples also contained 10–30 % mitragynine (our estimate from published chromatograms) (Philipp et al., 2011). Trakulsrichai et al. (2015) measured urinary mitragynine and reported levels “as low as 0.14% of mitragynine in an unchanged form” (Trakulsrichai et al., 2015). Lee et al. (2012) measured mitragynine in urine samples provided by the judiciary without any donor history (presumed to be kratom overdose victims) and found urinary mitragynine to vary between 0.004–150 μM and small amounts of 7-hydroxymitragynine. Two phase I metabolites were also detected in small and variable amounts. These studies show that mitragynine is extensively metabolized and an uncertain amount of mitragynine is directly excreted (Le et al., 2012).

For effect of mitragynine on metabolic enzymes, mitragynine enhanced expression of CYP1A2, CYP3A4, CYP2D6, and CYP2C9 (Hanapi et al., 2013; Lim et al., 2013; Manda et al., 2017), Table 2(c). Mitragynine induced CYP1A2 and weakly induced CYP3A4, as measured protein and mRNA expression (Lim et al., 2013). Substantially, identification on pregnane X receptor, which the transcription factor for P-gp and some CYPs, was also upregulated. However, a common enzyme inducer (aryl hydrocarbon receptor) was unaffected but mitragynine can induced CYP1A2 only (Manda et al., 2017). For instance, mitragynine can inhibited CYP2D6 and weakly inhibited some other CYP enzymes (Hanapi et al., 2013). However, the tested concentration employed unlikely to arise in plasma at doses used by human (see below). Other drug metabolizing enzymes, aminopyrine N-demethylase and glutathione S-transferase (Anwar et al., 2012), and uridine 5′-diphospho-glucuronosyltransferase (Haron and Ismail, 2015) showed weak effects and needed high concentrations Table 2(c). Regarding, the activity of mitragynine on P-gp was investigated by three studies (Manda et al., 2014, 2017; Meyer et al., 2015), Table 2(c). Those studies concluded that mitragynine can induced and inhibited P-gp; thus, co-adminstraiton of mitragynine with drugs which are P-gp substrated may possibly lead to occur drug-herbal interaction. Notably, when protein binding is considered, free mitragynine concentration and by extension

Table 2
In vitro metabolism and excretion of mitragynine.

(a): metabolic stability of mitragynine in rat or human liver microsomes or liver S9 fraction.

Model	Compound	Metabolic stability	Results	Reference
HLM	Mitragynine	% metabolized	30 %	(Manda et al., 2014)
Liver S9 fraction			55 %	
RLM	Mitragynine	% remained	84.5 ± 1.8 %	(Kong et al., 2017a)
	Propranolol[a]		21.4 ± 0.6 %	
	Verapamil[a]		69.0 ± 1.6 %	

(b): phase I and phase II metabolites of mitragynine, adapted from (Philipp et al., 2009)

Metabolites of mitragynine	Abbreviation
Phase I metabolites	
9-O-demethyl mitragynine	9-O-DM-MG, 2
16-carboxy mitragynine	16-COOH-MG, 3
9-O-demethyl-16-carboxy mitragynine	9-O-DM-16-COOH-MG, 4
17-O-demethyl-16,17-dihydro mitragynine	17-O-DM-DH-MG, 5
9,17-O-bisdemethyl-16,17-dihyro mitragynine	9,17-O-BDM-DH-MG, 6
17-carboxy-16,17-dihydro mitragynine	17-COOH-DH-MG, 7
9-O-demethyl-17-carboxy-16,17-dihydro mitragynine	9-O-DM-17-COOH-DH-MG, 8
Phase II metabolites	
9-O-demethyl mitragynine glucuronide	9-O-DM-G-MG, 2 G [a, b]
9-O-demethyl mitragynine sulfate	9-O-DM-S-MG, 2S [b]
16-carboxy mitragynine glucuronide	16-COOH-G-MG, 3 G [a, b]
9-O-demethyl-16-carboxy mitragynine glucuronide	9-O-DM-16-COOH-G-MG, 4 G [a]
9-O-demethyl-16-carboxy mitragynine sulfate	9-O-DM-16-COOH-S-MG, 4S [a, b]
17-O-demethyl-16,17-dihydro mitragynine glucuronide	17-O-DM-DH-G-MG, 5 G [b]
9,17-O-bisdemethyl-16,17-dihyro mitragynine glucuronide	9,17-O-BDM-DH-G-MG, 6 G [a]
9,17-O-bisdemethyl-16,17-dihyro mitragynine sulfate	9,17-O-BDM-DH-S-MG, 6S [b]

(c): effect of mitragynine on metabolic enzymes

Enzyme	Tested concentration of mitragynine	Results	Reference
Cytochrome P450-mediated metabolism of mitragynine			
CYP1A2	25 μM	Induction	(Lim et al., 2013)
CYP2D6		No induction	
CYP3A4		Weak induction	
CYP2D6	0.02 – 200 μM	Potent inhibitory (noncompetitive) IC_{50} = 0.4 ± 0.3 μM (K_i = 12.9 μM)	(Hanapi et al., 2013)
CYP3A4		Moderate inhibitory (competitive) IC_{50} = 41.3 ± 6.7 μM (K_i = 379.2 μM)	
CYP2C9		Moderate inhibitory (noncompetitive) IC_{50} = 9.7 ± 4.8 μM (K_i = 155.8 μM)	
CYP1A2	1 – 10 μM	Induction	(Manda et al., 2017)
CYP3A4		No induction	
Effect of mitragynine on the other drug metabolizing enzymes			
N-demethylase	0.25 – 250 μM	Induction	(Anwar et al., 2012)
glutathione S-transferase		Inhibition (IC_{50} = 11.8-24.4 μM)	
UGT	100 μM	Inhibition 4-methylumbelliferone glucuronidation in RLM, HLM, UGT1A1 and UGT2B7 (IC_{50} > 100 μM)	(Haron and Ismail, 2015)
Protein-mediated efflux transporters of mitragynine			
P-glycoprotein	5 – 10 μM	Inhibition	(Manda et al., 2014)
	5 μM	Inhibition	(Meyer et al., 2015)
	1 – 10 μM	Induction	(Manda et al., 2017)

Abbreviations: HLM = human liver microsomes; RLM = rat liver microsomes; CYP450 = cytochrome P450; UGT = uridine 5′-diphospho-glucuronosyltransferase; IC_{50} = half maximal inhibitory concentration; EC_{50} = half maximal effective concentration; K_i = inhibitory constant.
[a]Standard reference compounds of low and high metabolic stability.
[a]Metabolites of mitragynine could identified in urinary rats.
[b]Metabolites of mitragynine could identified in urinary humans.

the extracellular levels fall below the micromolar ranges and clearly well below those in Table 2(c). Thus, these actions on drug metabolism are mostly irrelevant to therapeutic or even toxic doses of mitragynine.

3.5. Pharmacokinetic studies of mitragynine in animals and humans

From our systematic reviewing process, five pharmacokinetic studies on mitragynine in rats were retrieved (de Moraes et al., 2009; Janchawee et al., 2007; Kong et al., 2017b; Parthasarathy et al., 2010; Vuppala et al., 2011). Among these studies, one rat study used a two compartment pharmacokinetic model (Kong et al., 2017b) while the others assumed a single compartment (de Moraes et al., 2009; Janchawee et al., 2007; Parthasarathy et al., 2010; Vuppala et al., 2011). Futhermore, one study determined about pharmacokinetics of mitragynine in human subjects (Trakulsrichai et al., 2015).

3.5.1. Intravenous administration of mitragynine to rats

Two studies reported on pharmacokinetics of intravenously administered mitragynine (1.5 and 5 mg/kg) into rats, presumably as a bolus (Parthasarathy et al., 2010; Vuppala et al., 2011), Table 3. The

Table 3
Pharmacokinetics of mitragynine in animals and humans.

Reference	Species	BW (g)	Sample	Dose (mg/kg)	Route (sampling)	Analytical method	LOD	LOQ	C_{max}	T_{max}	k_a	$AUC_{0-\infty}$	V_d, V_d/F	CL, CL/F	k_e	$t_{1/2}$
							μM**	μM**	μM**	hr	1/hr	μM/h**	L/kg	L/hr kg	1/hr	hr
Intravenous administration of mitragynine to rats (1.5-10 mg/kg)																
(Parthasarathy et al., 2010)	male SD rats	280-315	Plasma	1.5	i.v. (tail vein)	HPLC-UV	0.063	0.125	5.77 ± 3.01	1.2 ± 1.1	–	23.09 ± 16.31	0.79 ± 0.42	0.29 ± 0.27	–	2.9 ± 2.1
(Vuppala et al., 2011)	male SD rats	150-250	Plasma	5	i.v. (jugular vein cannula)	UPLC-MS	0.0005	0.0025	9.79 ± 1.76	1 min	–	8.53 ± 2.26	8.2 ± 2.2	1.2 ± 0.2	–	2.6 ± 0.4
(Kong et al., 2017b)	female SD rats	250-300	Dialysed plasma	10	i.v. (jugular vein)	UFLC-MS	–	0.025	[3.81 ± 0.38]	[0.5]	–	11.62 ± 1.10	9.84 ± 0.62	2.26 ± 0.21	0.24 ± 0.03	13.14 ± 1.42
			Brain ECF						[2.31 ± 0.13]	[0.5]	–	6.73 ± 0.35	16.94 ± 1.11	3.78 ± 0.18	0.23 ± 0.01	13.22 ± 2.55
Oral administration of mitragynine to rats (20-50 mg/kg)																
(Janchawee et al., 2007)	male Wistar rats	220-290	Serum	40	p.o. (orbital sinus)	HPLC-UV	0.075	0.251	1.58 ± 0.45	1.83 ± 1.25	1.43 ± 0.90	17.54 ± 7.35	89.50 ± 30.30	7.3[a]	0.07 ± 0.01	9.43 ± 1.74
(de Moraes et al., 2009)	male Wistar rats	200-250	Plasma	20	p.o. (decap-itation)	LC-MS/MS	–	0.0005	1.06	1.26	2.4	7.9	37.90	6.35	0.18	3.85
(Parthasarathy et al., 2010)	male SD rats	280-315	Plasma	50	p.o. (tail vein)	HPLC-UV	0.063	0.125	1.76 ± 0.53	4.5 ± 3.6	–	20.58 ± 7.53	64 ± 23	7.0 ± 3.0	0.105[b]	6.6 ± 1.3
Human subjects																
(Trakulsrichai et al., 2015)	Healthy volunteers	–	Plasma and urine	kratom tea***	p.o	LC-MS/MS	–	–	0.26[c]	0.83 ± 0.35	–	1.68[C]	38.04 ± 24.32	98.1 ± 51.34	–	~3 hr

** All values reported values in ug/mL have been converted to μM.
*** Kratom tea 60 mL (containing various concentration of mitragynine 6.25–11.5 mg) for 7 days and loading doses (6.25–23 mg) on days 8.
[x] These values are for unbound mitragynine, presumably excluding protein bound and each sample taken over 30 min.
[a]value convert unit from L/h to L/h kg.
[b]value has been calculated from formulation ($k_e = 0.693/t_{1/2}$).
[c]value has been found at highest loading dose (23 mg).
V_d/F and CL/F were apparent volume distribution and apparent total clearance that were calculated for oral administration.
Abbreviations:SD = Sprague-Dawley; BW = body weight; p.o. = per oral; i.v. = intravenous; ECF = extracellular fluid; HPLC-UV = high performance liquid chromatography coupled to ultra-violet; LC–MS/MS = high performance liquid chromatography coupled to tandem mass spectrometry; UPLC-MS = ultra-performance liquid chromatography coupled with a mass spectrometer; UFLC-MS = ultra-fast liquid chromatography equipped with a mass spectrometer; LOD = limit of detection; LOQ = limit of quantification; C_{max} = maximum serum/plasma concentration; T_{max} = time to reach maximum concentration; k_a = absorption rate constant; $AUC_{0-\infty}$ = area under the curve from time equals zero to infinity; V_d = volume distribution; CL = clearance; k_e = elimination rate constant; $t_{1/2}$ = half-life.

Table 4
Quality assessment of pharmacokinetic studies of mitragynine.

No.	Main domain	Sub-domains	(Janchawee et al., 2007)	(de Moraes et al., 2009)	(Parthasarathy et al., 2010	(Vuppala et al., 2011)	(Kong et al., 2017b)	(Trakulsrichai et al., 2015)
1	Title and abstract	Title identified the compound, species, administration route. Abstract includes all key information of domains 2-12 and key numerical data.	Y/N	Y	Y/N	Y/N	Y	Y
2	Background, objectives	Scientific background and explanation of the rationale, clear objectives, hypotheses, and usefulness.	Y	Y	Y/N	Y/N	Y	Y
Methods								
3	Participants, subjects	Appropriate selection criteria, sample size, and recruitment.	Y	Y	Y/N	Y	Y	Y/N
4	Approvals	Full complied with ethical and safety standards and approvals.	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
5	Design and protocols	Adequately spaced sampling of blood, and includes urine and fecal samples. Appropriate design. Appropriate dose.	Y/N	Y/N	Y/N	Y	Y	Y/N
6	Procedures	Subject depositions and sampling methods. Enough detail to permit study replication.	Y/N	Y	Y	Y	Y	Y/N
7	Chemical assays	Suitable standards and extraction controls including 'spiking', sensitivity, reproducibility, and selectivity.	Y	Y	Y	Y	Y	Y
Results								
8	Flow	Flow experienced by each participant/animal.	N	N	N	N	N	N
9	Data reporting	Reporting adequate; availability of raw data.	N	N	N	N	N	N
10	Baseline data	Baseline demographics that might influence pharmacokinetics.	NA	NA	NA	NA	NA	Y/N
11	Analysis	Data and analysis adequately extracted key pharmacokinetic parameters and statistic where appropriate. Described data pooling.	Y	Y	Y/N	Y	Y	Y/N
Discussion and conclusions								
12	Interpretation	Relating the key biological factors to pharmacokinetics and predictable clinical outcomes. Generalizability of results. Validation on conclusion.	Y/N	Y/N	N	Y/N	Y/N	Y/N
	Mean overall score, %		59%	68%	45%	64%	73%	54%

Abbreviation: NA = Not appropriate. Scoring: complete domains attracted a "Y" score = 1; some missing formulation was "Y/N" score 0.5; missing information prevented the reader from drawing conclusion was given "N" score = 0.

maximal plasma concentration (C_{max}) was 10 μM at time to reach maximum concentration (T_{max}) of 1 min (Vuppala et al., 2011) but Parthasarathy et al. (2010) either missed T_{max} by late sampling or it was very delayed (C_{max}˜6 μM at T_{max}˜70 min) (Parthasarathy et al., 2010). Parthasarathy et al. (2010) used a robust cross-over design but measurements may have been compromised by using the tail vein for sampling.

Kong et al., (2017) used the same injection protocol but sampled by dialysis tubing from blood and brain but temporal resolution was slow because of 30 min sampling periods (Kong et al., 2017b). The C_{max} in blood was 3.8 μM which equates to ˜38 μM for whole plasma assuming 90% protein binding. Volume distribution (V_d) was 9.8 L/kg and half-life ($t_{1/2}$˜13 h) was much longer than the other intravenous studies. For brain, C_{max} was lower (2.3 μM) and V_d was higher (17 L/kg) than blood. AUC_{brain}/AUC_{plasma} was 0.66, indicating substantial penetration of the blood-brain barrier and tissue loading.

3.5.2. Oral administration of mitragynine to rats

Three studies reported on pharmacokinetics of orally administered mitragynine (20–50 mg/kg) in rats (de Moraes et al., 2009; Janchawee et al., 2007; Parthasarathy et al., 2010) (Table 3). The pharmacokinetic studies serially sampled with time from each animal, except de Maoraes et al., (2009) who used 8 animals, a protocol suited to tissue collection. Here, there was less variation than between intravenous studies and C_{max} (1–1.8 μM) appeared linearly related to dose. Mitragynine was rapidly absorbed with T_{max}˜1.5 h; although Parthasarathy et al. (2010) had no characteristic well-defined peak in the reported pooled data. The oral bioavailability of mitragynine was calculated by (Parthasarathy et al., 2010), indicating as low oral bioavailability (F˜3%). However, the area under the curve (AUC) values and intravenous dosing from the study (Vuppala et al., 2011) and oral dosing from the study (de Moraes et al., 2009) both who had reliable sampling blood methods, sampling times, and assay procedures that allowed us to calculate F as ˜21%.

3.5.3. Oral administration to humans

Mitragynine pharmacokinetics were studied in ten men having a history of kratom abuse (Trakulsrichai et al., 2015). They were randomly divided into five unequal groups and given daily conditioning doses of kratom tea containing 6.25–11.5 mg of mitragynine for 7 days. On day 8, participants were given a single oral dose of kratom tea standardized for mitragynine contents (6.25–23 mg), then blood and urine sampled over 24 h. For plasma mitragynine, C_{max} and AUC values (Table 3) suggested dose dependency but the data were too scattered and underpowered for a definitive conclusion. The declines were mostly bi-exponential so a two-compartment pharmacokinetic model was assumed. The average apparent V_d was 38.0 ± 24.3 L/kg and clearance (CL) was 98.1 ± 51.3 L/hr/kg. Time-plots were shown for each participant and for 6 records, the baseline plasma mitragynine concentrations were similar to those after 24 h. Graph crowding made it difficult distinguish other records. Two participants displayed a maintained plateaued plasma concentration. Reader is not informed of the test and conditioning doses used for each participant.

3.6. Quality assessment of pharmacokinetic studies

Six pharmacokinetic studies were assessed for their quality (Table 4). The protocols were fundamentally similar but without adequate reporting the causes of differences in pharmacokinetic variables were unclear.

For intravenous administration, only Vuppala et al. (2011) began sampling quickly after injection (1 min) while other studies of Parthasarathy et al. (2010) sampled too late to capture C_{max}. Kong, Mohamed, et al., (2017) were restricted to 30 min periods of slow sampling of dialysate. Particularly, crucial details about drug administration and specially sampling were scant; except in study of Vuppala et al. (2011) which stands out as the most reliable study by injecting and sampling from a large venous cannula that a method suited for small animal pharmacokinetic studies with many sampling times.

For oral administration, animals deprived of food and dosed with a variety of mitragynine formulations (100% propylene glycol; pH 4.7 acetate; 20% Tween 80) that are likely to impact on absorption especially the dispersing agents. Animals were anaesthetized or free-ranging or unreported. Different activity levels and particular high blood flow to active tissues probably promotes re-distribution. de Moraes et al. (2009) sampled blood by decapitation thus ideally able to follow tissue levels of mitragynine also having ample blood to measure at least key metabolites by LC/MS but did not do so. Only Trakulsrichai et al. (2015) provided data for each participant but could be related to dose (see above) and no study provided raw data. Raw data shows the sources of variability and allows verification of data-analysis. Raw data for the Parthasarathy et al., (2009) study may have explained the apparently flat concentration time curve after oral administration and for the delayed C_{max} with both routes of mitragynine administration. Had urinary pH and creatinine been measured by Le et al., (2011) and Trakulsrichai et al. (2015) disparate urinary mitragynine concentrations might have been explained. Only study by Trakulsrichai et al. (2015) focused on pharmacokinetics while other studies used pharmacokinetics as an adjunct to describing assay methods which in some cases occupied nearly all abstracts, a common strategy in herbal medicinal chemistry. Notwithstanding the above, most deficiencies arose from adhering to laxed reporting standards prevailing at the time of execution.

In vitro studies were not systematically screened for quality but the concentrations used exceeded high concentration levels of mitragynine up to 200 μM, a problem that is rife in herbal medicine research. Thus, although many drug metabolism enzymes were modified by mitragynine only a few effects are translatable to its therapeutic application.

4. Discussion

A substantial amount of data relevant to the pharmacokinetics of mitragynine has been published. Being a weak base, mitragynine absorption is moderately rapid at physiological pH in the distal small intestine and appears to be passive. Like most weak bases, it diffuses as the unionized form into the cytosol. The drug then becomes ion-trapped by the lower cytosolic pH, leading typically to a 6-fold concentration compared to the extracellular levels (Brown and Garthwaite, 1979). The uncharged form can also partition into fat stores but tendency is reduced in the more acidic cytosol surrounding most lipid deposits. This explains the high V_d of weakly basic drugs including mitragynine. Thus, filling this large sink can account for much of the initial decline. This justifies at least a two-compartment pharmacokinetic model. The 85–95 % plasma protein binding introduces two complications: (i) the effective mitragynine concentration in extracellular space is approximately 10% of the measured plasma concentration lowering activation of membrane receptors and concentration dependent diffusion; and (ii) the calculated V_d value can be lowered.

Mitragynine metabolism also influences $t_{1/2}$ predominantly by conjugation but also phase I modifications that contributed to excreted mitragynine. No discovered study could delineate contributions of metabolism, excretion, and redistribution to $t_{1/2}$ making it difficult to predict drug clearance for any particular person. An important variable is urinary pH, that normally varies between 4.6 and 8.0, could account for up to a 100-fold range of mitragynine excretion as a weak base. Thus measuring urine volume, pH, creatinine provides all the data to assess drug excretion but no study performed these. To date, contribution of phase I and phase II drug metabolizing enzyme on mitragyine has been established. Consequently, when co-administered mitragynine with other drugs, which extensively metabolized by these enymzes as described above, intreaction herbal-drug might be possible.

No study assessed tissue levels of mitragynine over time as a guide to redistribution. While perfusion rates are fairly constant for brain, kidney, liver, other tissues (gut and muscle) have highly variable perfusion rates; hence, the rate and size of the redistribution pool may be highly variable and impact on $t_{1/2}$. Therefore, the pharmacokinetics are complex and the studies so far have provided incomplete data. The pharmacokinetic studies in rat were similar to those in the human study except for lower C_{max} in humans (range 45–300 nM, cf 1500 nM in rats). The fast T_{max} of 0.8 h in human compared with ~1.5 h in rat suggests that simple dissolution in the aqueous media fed to humans without dispersing agents is enough for fast absorption. The different C_{max} reflects higher oral doses (20–50 mg/kg) given to rats (body weight: 0.22 − 0.32 kg). These equate to 220–550 mg in human (70 kg) using allometric scaling from rats (Sharma and McNeill, 2009), doses regarded as toxic in humans. Thus studies on human cell lines *in vitro* or human proteins should aim for actions evoked at submicromolar concentrations.

Pharmacokinetic parameters of mitragynine in rats show some variability between studies. For intravenous delivery, only Vuppala et al. (2011) began early enough to obtain a near true C_{max} while Kong, Mohamed et al. (2017) started sampling at 30 min and Parthasarathy et al. (2010) started at 20 min. The latter authors using tail vein also obtained a delayed C_{max}, suggesting either slow drug infusion or poor mixing. Their volume distribution was atypically low for a diffusable weak base and far lower than the two other intravenous studies. These questions about the Parthasarathy et al. (2010) data and their low 3% bioavailability determination is also worrisome. Due to its lipophilicity and poor water solubility at physiological pH, mitragynine can be classified as Class II Drug according to the Biopharmaceutical Classification System (BCS) (Sachan et al., 2009). Dissolution is one of the major factors influencing mitragynine oral bioavailability. A slow dissolution rate may play an important role in its low bioavailability (Barthe et al., 1999). Therefore, a development of an appropriate salt form of mitragynine may be able to increase its bioavailability oral. Our determination of 21% using data deemed as the most reliable accords with other diffusible weak bases including codeine which has a similar single pKa to mitragynine, undergoes extensive metabolism, additional polar (−OH) group, high V_d, and high bioavailability of > 50%. The remaining 80% of ingested mitragynine is either first-pass metabolized, remains in the gut unchanged, or degraded by the microbiota which is common with herbal medicines. Feces determination could help resolve this question. This is important because heterogeneity of the human microbiota can influence potency enormously.

We also designed a quality assessment which arose from a careful in-depth analysis of the discovered papers which lead to the guidance notes listed in supplement S1. Such detailed assessment tools should be mandatory for all systematic reviews if their conclusions are to be reliable. The PRISMA statement should be updated to account for this increased assessment rigor and extended to animal studies.

These studies leave many questions unanswered. Our quality assessment tool found some studies had poor design, execution, and laxed reporting creates confusion. Production of metabolites that are also biologically active or toxic were not considered. Nevertheless, one well-designed robust animals and human study could provide all the missing data, except concentration-time courses of mitragynine in organ tissues (i.e. brain, fat, muscle, kidneys, liver) would need an animal study as well as studies involving roles of protein transporter in mitragynine disposition. These new results from the studies are possibly explain more about pharmacokinetic behaviors of mitragynine.

5. Conclusion

This systematic review found several pharmacokinetic studies on mitragynine which varied in reporting, reliability, and completeness. While crude changes in blood levels after oral mitragynine can be modelled. The data on metabolism and excretion cannot be applied to humans. Future studies on mitragynine and other medicine should fully report methods, data, adhere to ethics, and maximise data collection. This includes a full 48 h blood time course including major metabolites, urinalysis of the agent and metabolites, fecal samples and a bioavailability determination. Nonetheless, the available information regarding the pharmacokinetics of mitragynine is not complete. For example, metabolism of the compound, bioavailability problem, disposition of this compound in the other tissues, mode of protein transporter into the brain, and potential interactions with other drugs or chemicals. There gaps of knowledge need further research.

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Contributions

Study concept and design: Ms. YA, Dr. Methaneethorn, and Dr. Lohitnavy

Drafting of the manuscript: Ms. YA, Dr. Methaneethorn, and Dr. Lohitnavy

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Writing of the manuscript: Ms. YA

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Critical revision of the manuscript: Dr. Scholfield, Dr. Methaneethorn, and Dr. Lohitnavy

Conflict of interest

No conflict declared

Author disclosures

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Appendix A. Supplementary data

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