Pharmacokinetics and pharmacodynamics of mitragynine, the principle alkaloid of Mitragyna speciosa: present knowledge and future directions in perspective of pain

Abstract: Mitragyna speciosa, commonly known as Ketum or Biak in Malaysia and Kratom in Thailand, is a native plant to Southeast Asia and has various pharmacological benefits. Mitragynine (MG) is the principal alkaloid found in the leaves of Mitragyna speciosa and has been reported to be responsible for the plant’s therapeutic actions. Traditionally, local communities use Kratom preparations for relief from different types of pain. The potential analgesic effects of MG using rodent models have been reported in literatures. We have reviewed the published analgesic and pharmacokinetic studies and all of these findings showed the routes of drug administration, doses employed, and type of vehicles used to solubilize the drug, varied considerably; hence this posted difficulties in predicting the drug’s pharmacokinetic-response relationship. A rational approach is warranted for accurate prediction of dose-response relationship; as this is essential for the development of MG as an alternative medicinal drug for pain management. PKPD modeling would serve as a better method to understand the dose-response relationship in future MG preclinical and clinical studies.

Keywords: Mitragyna speciosa, mitragynine, pain, pharmacodynamics, pharmacokinetics, physicochemical

DOI: 10.1515/jbcpp-2019-0138

Received: June 5, 2019; Accepted: August 15, 2019

Introduction

The Mitragyna speciosa plant locally known as Ketum or Biak in Malaysia [1], [2] and Kratom in Thailand, is a member of the Rubiaceae family. This plant is native to Southeast Asia. Mitragyna speciosa has been employed as a stimulant as well as a remedy for various physical and mental illness [3], [4]. Numerous studies have reported the traditional uses of Kratom among rural folk, peasants, and laborers in Southeast Asia [5], [6]. Its usage in US and Europe is widespread and it is accessed easily via online merchants or in physical retail stores in different forms such as dried or powdered leaves in bulk or in capsules, tablets, and other extracts [7], [8], [9], [10]. It has medicinal values to treat various ailments, but importantly to wean off opiate drug users from withdrawal symptoms [1]. This is because Kratom is believed to be a “safe” herbal drug showing medicinal importance in the West [11], [12].

Kratom preparations are sold in the United States and several European countries through online merchants or in physical retail stores in different forms as mentioned above. Fresh Kratom leaves can be consumed by chewing, smoking, or ingesting orally by brewing as a tea or juice [13] to minimize fatigue, enhance work performance, and improve physical tolerance to heavy workload [14], [15]. It is widely used to treat conditions or ailments such as muscle pain, intestinal infection, cough, diarrhea, fever, and as an appetite-suppressing agent or anti-depressant [1]. Besides its therapeutic effects, Kratom is also an affordable opiate substitute among drug users in rural areas in the northern states of Malaysia. In view of addiction, this plant is mainly used to reduce illicit drug dependency and suppression of withdrawal symptoms.
Approximately 40 alkaloids have been discovered in *Mitragyna speciosa* leaves. The alkaloid content in the leaves depends on the geographical regions and seasons of harvest [16]. Its main active alkaloid, mitragynine (MG) was found to have a unique morphine like-effects or opioid receptor agonist effects on guinea-pig ileum [17]. Its minor constituent 7-hydroxy MG inhibited electrically induced contractions through opioid receptors in guinea-pig ileum, and its effects was about 13 times more potent than morphine. MG is the most abundant active alkaloid derived from the leaves of *Mitragyna speciosa*, which constitutes up to 66% of total alkaloid mixture.

The clinical efficacy of a drug therapy is determined by its pharmacokinetic (PK) and pharmacodynamic (PD) profiles. Although, the pharmacological effects of Kratom in human and experimental animals are well-established, the pharmacokinetics and toxicity data of pure MG and alkaloid extract still remain poorly defined. This article reviews the interplay between pharmacokinetics and pharmacodynamics of MG (i.e. dose-exposure-response relationships) with the physicochemical characterization of MG, which will provide a basis for developing a suitable formulation to further improve its solubility, stability and oral absorption for better assessment of this compound in preclinical and clinical studies.

### Physicochemical properties or characterization

MG has both hydrophobic and lipophilic properties (log P 1.76) [18]. It is a weak base (pka 8.3) and poor water solubility (<100 μg/mL). It is highly soluble in acidic condition but acid-degradable. In simulated gastrointestinal fluid studies, MG showed incomplete dissolution in simulated intestinal fluid (SIF) but stable. However, the drug demonstrated good solubility in simulated gastric fluid (SGF) but acid-degradable (~20%) [18], [19]. Recent studies reported MG as a poorly soluble drug with high permeability, a dose of 40 μg/mL has high intestinal permeability drug in rats using in situ absorption model [20]. Studies also found that MG was not affected by P-glycoprotein efflux effect and cytochrome P3A4 which are associated with low permeability [20], [21].

### Nonclinical vehicle use in studies

The use of appropriate vehicles to solubilize drug or extracts prior to oral or parenteral administration is vital in preclinical animal studies. Any drug to be absorbed must be present in the form of solution at the site of absorption; hence various vehicles were used to facilitate the solubility of MG. The vehicles commonly used to facilitate the solubility of MG were 1% cremophor in saline, 1% acetic acid (pH 4.7) or propylene glycol, 4% acacia gum, Tween 20, Tween 80 [22], [23], [24]. In most instances upon solubilizing, the drug will be either in the form of solution or suspension depending upon the dosage employed in preclinical studies. However owing to its basic sub-optimal physicochemical properties, this drug predominately exists in ionic form in gastric juice and encounter solubility issue in the intestinal fluid. Thus, there are high possibility of MG being aqueous, basic in nature and moderate lipophilic characteristic. Apart from the solubility, intestinal permeability of a drug also attributes to its bioavailability. In case of MG, it has showed a high intestinal permeability in animal model. On an average, the sub-optimal physicochemical properties of MG and difference in vehicles utilized may contribute to the higher variation and conflicting qualities in PK-parameters. PKPD modelling is essential to overcome these drawbacks.

### Pharmacokinetics of MG

The pharmacokinetics of MG after oral and intravenous administration in rats was limited. As of date only one pharmacokinetic study of MG in human (Kratom users) was documented in literature [22]. In rats, investigators reported a large variation in the C\text{max} (0.42–0.70 μg/mL), t\text{max} (1.26–4.50 h) and elimination half-life (3.85–9.43 h\textsuperscript{−1}) of MG after oral administration. Both CL/F (apparent total clearance) and Vd/F (apparent volume of distribution) showed inconsistent findings, where CL/F (1.6–7.0 L/h/kg) and Vd/F (37.90–89.5 L/kg) [23], [24], [25].

Apart from studies on MG’s pharmacokinetic profile in animal model, recently Trakulsrichai and colleagues reported human pharmacokinetic study with two loading doses of Kratom tea. This was the first study on the pharmacokinetic parameters from the nine existing Kratom users using non-compartmental analysis, where t\text{max} was 0.83 ± 0.35 h, with terminal half-life at (23.24 ± 16.07 h), and the apparent volume of distribution (38.04
± 24.32 L/kg). The unchanged form found in the urine was 0.14% with the clearance rate of 98.1 ± 51.34 L/h/kg [22]. The overall studies have been summarized in Table 1.

Table 1: Pharmacokinetic studies of MG.

<table>
<thead>
<tr>
<th>Species</th>
<th>MG dose, mg/kg</th>
<th>Cmax, μg/mL</th>
<th>Tmax, hours</th>
<th>t½, hours⁻¹</th>
<th>Clearance, L/h/kg</th>
<th>Volume of distribution-Vd/F, L/kg⁻₁</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>40 [p.o.] [Vehicle: 100% propylene glycol]</td>
<td>0.63 ± 0.18</td>
<td>1.83 ± 1.25</td>
<td>9.43 ± 1.74</td>
<td>1.60 ± 0.58</td>
<td>89.50 ± 30.30</td>
<td>Janchawee et al. [23]</td>
</tr>
<tr>
<td></td>
<td>20 [p.o.] [Vehicle: 1% acetic acid]</td>
<td>0.42 ± 61.79</td>
<td>1.26 ± 0.02</td>
<td>3.85 ± 0.51</td>
<td>6.35 ± 0.43</td>
<td>37.90 ± 5.41</td>
<td>de Moraes et al. [24]</td>
</tr>
<tr>
<td></td>
<td>1.5 [iv] [Vehicle: 20% Tween 20]</td>
<td>2.3 ± 1.2</td>
<td>1.20 ± 1.1</td>
<td>2.9 ± 2.1</td>
<td>0.29 ± 0.27 (absolute)</td>
<td>0.79 ± 0.42</td>
<td>Parthasarathy et al. [25]</td>
</tr>
<tr>
<td></td>
<td>50 [p.o.] [Vehicle: 20% Tween 20]</td>
<td>0.7 ± 0.21</td>
<td>4.5 ± 3.6</td>
<td>6.6 ± 1.3</td>
<td>7.0 ± 3.0</td>
<td>64 ± 23</td>
<td>Parthasarathy et al. [25]</td>
</tr>
<tr>
<td>Humans</td>
<td>Loading dose [p.o] [vehicle: distilled water]</td>
<td>0.83 ± 0.35</td>
<td>23.24 ± 16.07</td>
<td>98.1 ± 51.34</td>
<td>38.04 ± 24.32</td>
<td>Trakulsirichai et al. [22]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High: 23</td>
<td>0.105</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low: 6.25</td>
<td>0.0185</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pharmacokinetic studies of MG.

Since there are limited animal studies and only one human study on PK of MG, there was a challenge in the selection of appropriate dose for further investigations. From all these pharmacokinetic studies, the range of the dose employed varied significantly. These variations were observed in both preclinical and human studies. Apart from the dosing, different routes of administration and extraction methods also contribute to the variability in pharmacokinetic data.

Pharmacodynamics of MG (anti-nociceptive or analgesic)

Opioids have been used extensively in treating pain for more than 100 years. Opioid receptors can be classified into three subtypes which are Mu (μ), kappa (κ), and delta (δ) opioid receptors [26]. With regards to MG, high affinity was found towards κ-opioid receptors followed by μ- and δ-opioid receptors [27]. It acts as a receptor agonist at μ-opioid receptors and possibly as an antagonist at κ-opioid receptors [28], [29], [30]. At cellular level, MG blocks neuronal Ca²⁺ channels [31]. It was also found to inhibit forskolin-stimulated cyclic adenosine monophosphate (cAMP) formation in vitro in an opiate receptor-dependent way [32], [33]. Expression of cAMP and cAMP response element-binding protein (CREB) was reported due to repeated exposure of MG [34]. Twitch contraction of the ileum of the guinea pig occurred with the aid of electrical stimulation to assess the agonistic action of the opioid receptor. Opioid agonist activity is measured as the inhibition of the twitch contraction, which is reversed by the opioid receptor antagonist naltrexone. Mitragyna speciosa preparations, MG, and other isolated Mitragyna speciosa indole alkaloids as well as MG derivatives result in the inhibition of the electrically stimulated contraction. However, MG was 10 times lesser potent than morphine [17], [35].

Till date, all of the reported analgesic or anti-nociceptive studies were only performed on animal models and not on humans. Various behavioral tests and different range of doses gives a drawback mainly to compare the effective dose for analgesic or anti-nociceptive activity.

Pain assessment of Kratom was evaluated using well established behavioral test. In late 90s, Matsumoto and his colleagues discovered the anti-nociceptive properties of MG in mice using several behavioral tests such as hot plate, tail pinch and 5-Methoxy-N,N-dimethyltryptamine-induced twitch and weavng responses [36], [37].

Idid et al. reported that the anti-nociceptive action of MG at 200 mg/kg was less prominent comparable to the morphine (5 mg/kg) and more effective compared to 100 mg/kg paracetamol in acetic acid induced writhing, and the hot and cold tail-flick tests [38]. The mechanism of paracetamol is mainly focused on COX
inhibition (peripheral) and non-opioid (central) pathway which limits the comparison of the analgesic activity between MG and paracetamol [39].

Antinociceptive effects was observed after oral administration of *Mitragyna speciosa* preparations. Methanolic and alkaloid *Mitragyna speciosa* extracts extended the inactivity of a nociceptive response to noxious stimulation in the hot-plate test, but not in the tail-flick test [40]. This finding showed that *Mitragyna speciosa* extracts most likely act on the central pathway which is indicated by analgesic response in hot plate test [41]. With regards to synergism, *Mitragyna speciosa* alkaloid extract administered with caffeine and codeine improves the anti-nociceptive effect in a hot plate test with rats [42].

Following these outcomes, Shaik Mossadeq et al. conducted study where methanolic extract of *Mitragyna speciosa* yielded to anti-nociceptive responses in hot-plate, acetic-acid-induced writhing and the formalin tests in mice [43]. Thereafter, it was shown by Sabetghadam et al. and Takayama et al. that different extracts of *Mitragyna speciosa* (alkaloid, methanolic, and aqueous) and MG derivatives significantly prolonged the latency of nociceptive responses compared to the morphine in both hot-plate and tail flick tests in rats. The pre-administered-opioid antagonist naloxone abolished effects of *Mitragyna speciosa* extracts, which suggest that the extracts act through opioid-receptor [44], [45].

Recently, Criddle compared the effect of 300 mg/kg of extracts, 75 mg/kg of alkaloids fraction, and 30 mg/kg of MG of *Mitragyna speciosa* with opioid agonists; 10 mg/kg morphine and 3 mg/kg oxycodone, in rats using hot plate method. This study showed that intraperitoneal and oral administration of MG produce antinociceptive effects equivalent to the reference opioid agonists [46], [47]. The overall study has been summarized in Table 2.

**Table 2: Pharmacodynamic studies of mitragynine (anti-nociceptive/analgesic).**

<table>
<thead>
<tr>
<th>Compound/extract</th>
<th>Species</th>
<th>Behavioural test/In vitro models</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitragynine [5–30 mg/kg, i.p.], [1.0–10.0 μg/mouse]</td>
<td>Male ddy Mice</td>
<td><em>Antinociceptive</em></td>
<td>Matsumoto et al. [36]</td>
</tr>
<tr>
<td>Mitragynine [1–30 mg/kg, i.p.]</td>
<td>Male ddy mice</td>
<td><em>Antinociceptive</em></td>
<td>Matsumoto et al. [37]</td>
</tr>
<tr>
<td>Mitragynine [10 μm]</td>
<td>Guinea Pig</td>
<td><em>Analgesic</em></td>
<td>Watanabe et al. [17]</td>
</tr>
<tr>
<td>– Methanolic extract</td>
<td></td>
<td>Electrically stimulated contraction of ileum</td>
<td></td>
</tr>
<tr>
<td>– Mitragynine</td>
<td></td>
<td></td>
<td>Horie et al. [35]</td>
</tr>
<tr>
<td>Mitragynine [200 mg/kg, p.o.]</td>
<td>Albino mice</td>
<td><em>Analgesic</em></td>
<td>Idid et al. [38]</td>
</tr>
<tr>
<td>Methanolic extract [50, 100, 200 mg/kg, p.o.]</td>
<td>Mice, Rat</td>
<td><em>Antinociceptive</em></td>
<td>Reanmongkol et al. [40]</td>
</tr>
<tr>
<td>Alkaloid extract [5, 10, 20 mg/kg, p.o.]</td>
<td></td>
<td>Hot plate test and tail pinch test</td>
<td></td>
</tr>
<tr>
<td>Methanolic extract [100, 200 mg/kg, i.p.]</td>
<td>Mice</td>
<td></td>
<td>Shaikh Mossadeq et al. [43]</td>
</tr>
<tr>
<td>Methanolic extract [50, 100, 200 mg/kg, p.o.]</td>
<td>Rats</td>
<td><em>Antinociceptive</em></td>
<td>Sabetghadam et al. [44]</td>
</tr>
<tr>
<td>Alkaloid extract [5, 10, 20 mg/kg, p.o.]</td>
<td></td>
<td>Hot plate test and tail flick test</td>
<td></td>
</tr>
<tr>
<td>Aqueous extract [100, 200, 400 mg/kg, p.o.]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitragynine derivatives [icv] Intracerebroventricular</td>
<td>Mice</td>
<td><em>Analgesic</em></td>
<td>Takayama et al. [45]</td>
</tr>
</tbody>
</table>

- | - | - | - | -
Methanolic extract [300 mg/kg, p.o.]
Alkaloid extract [75 mg/kg, p.o.]
Mitragynine [10 mg/kg, p.o. and i.p.]

| Rat | Antinociceptive Hot Plate test | Criddle [46] | Carpenter et al. [47] |

Pharmacodynamic studies of MG.

**Routes of administration**

Important factors in the determination of PK and PD relationship in MG include the routes of administration. Till date, MG and several Kratom extracts have been administered via oral, intra peritoneal, and intravenous routes to explore MG’s PK profiles and its analgesic effects individually [22], [25], [40]. These studies are insufficient to provide comprehensive relationship between PK and PD. This is because different routes affect the concentration level reaching the target tissue and subsequent analgesic activity [48]. Thus, future studies on the effects of various routes of administration on both PK and PD are recommended in order to ascertain the role of the different routes in exploring the bioavailability of MG.

**PKPD modeling study**

The rationale of PKPD-modeling is to link pharmacokinetics and pharmacodynamics in order to establish and evaluate dose-concentration-response relationships and subsequently describe or predict the effect-time courses resulting from a drug dose [49].

Pain perception is characterized by multiple factors, thus PKPD modeling becomes too intricate to discover the analgesic drugs. Moreover, limited responders to experimental pain model and analgesic drugs lead to difficulty in obtaining data for PKPD modelling [50].

In some cases, the analgesic effects of opioid drugs were not correlated with its plasma concentration and time-course of the effects [51]. For example, alfentanil and its derivatives show rapid transfer between plasma concentrations to its effect site while morphine and buprenorphine demonstrates contrary effects [52], [53]. On the other hand, active metabolites also have shown to contribute analgesic/anti-nociceptive activity. Morphine is the active metabolite of codeine whereas morphine-6-glucuronide for morphine and M1 metabolite for tramadol [54], [55], [56]. As for MG, the principal alkaloid of Kratom has similar effects to opioid drugs. Also, there are many factors associating with PKPD modeling of these class of analgesic drugs. The typical PK parameters of active ingredients in a single herb or complex herbal formulation could not fully describe the mechanism actions of herbal medicines which correspond to its PD. With regards to this, PKPD modeling have been used to investigate the safety and the effectiveness of the herbal medicines as well as herb-herb synergistic effects in herbal medicines [57], [58], [59]. An example, glycyrrhetinic acid with paeonilfiorin is an active ingredient in liquorice decoction have been demonstrated to work synergistically as analgesic to treat dysmenorrhea using PKPD modeling [59]. Considering all the above points, development of PKPD modeling for MG with respect to dose design and the interaction of its analgesic properties are required.

**Conclusions**

Based on the above reports, we conclude that MG has sub-optimal physicochemical properties which could be a challenge in the development of a desirable formulation that can be used for future preclinical and clinical studies. PKPD has become an integral part of the development of designing a new formulation. However, there have not been studies reporting on the correlation between PK and PD of MG in humans as well as animal models. Because of the addiction property of Kratom, determination of safe dose is crucial for human consumption. Importantly, this is the limitation to predict the effective dose of MG with less adverse effects for the pain treatment. Therefore, PKPD modeling is essential for the development of MG as an analgesic/anti-nociceptive drug at a safe dose for human wellbeing.
Funding

Financial support was received from Higher Education Centre of Excellence (HiCoE) special funding (311/C-DADAH/4401009). The University Sains Malaysia (USM) funded Dinesh Sangaran Ramachandram through USM Fellowship program.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

References


