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REVIEW ARTICLE

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A systematic review of (pre)clinical studies on the therapeutic potential and safety profile of kratom in humans

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Abstract

Introduction: Kratom *(Mitragyna speciosa)* is a tropical plant traditionally used as an ethnomedicinal remedy for several conditions in South East Asia. Despite the increased interest in its therapeutical benefits in Western countries, little scientific evidence is available to support such claims, and existing data remain limited to kratom's chronic consumption.

Objective: Our study aims to investigate (pre)clinical evidence on the efficacy of kratom as a therapeutic aid and its safety profile in humans.

Methods: A systematic literature search using PubMed and the Medline database was conducted between April and November 2020.

Results: Both preclinical (N = 57) and clinical (N = 18) studies emerged from our search. Preclinical data indicated a therapeutic value in terms of acute/chronic pain (N = 23), morphine/ethanol withdrawal, and dependence (N = 14), among other medical conditions (N = 26). Clinical data included interventional studies (N = 2) reporting reduced pain sensitivity, and observational studies (N = 9) describing the association between kratom's chronic (daily/frequent) use and safety issues, in terms of health consequences (e.g., learning impairment, high cholesterol level, dependence/withdrawal).

Conclusions: Although the initial (pre)clinical evidence on kratom's therapeutic potential and its safety profile in humans is encouraging, further validation in large, controlled clinical trials is required.

KEYWORDS
adverse effects, kratom, mitragynine, opioid withdrawal, pain, therapeutic benefits

1 | INTRODUCTION

Kratom (*Mitragyna speciosa*, Rubiaceae family) is an indigenous tropical tree from Southern East Asia (e.g., Malaysia, Thailand, Laos, Cambodia), which also grows in East-West Africa and Papua New Guinea (Hassan et al., 2013; Kruegel and Grundmann, 2018). This evergreen non-seasonal plant is also known locally with other names, such as *Biak-Biak*, *Ketum*, *Kakuam*, *Ithang*, *Thom*, and *Mambog* (Hassan et al., 2013; Veltri and Grundmann, 2019). It exerts stimulant cocaine-like effects in doses smaller than 5 g and sedative-like effects

at higher doses between 5 and 15 g (Cinosi et al., 2015; Eastlack et al., 2020).

Kratom leaves are generally smoked, chewed, or brewed as an herbal decoction (Hassan et al., 2013; Kruegel and Grundmann, 2018). It has been used traditionally for centuries to treat several medical conditions like diarrhea and pain, to mitigate opioid and alcohol withdrawal symptoms, to detoxify from other substances, like cannabis or methamphetamine, to improve sexual desire, and to combat fatigue (Grewal, 1932a; Hassan et al., 2013; Saref et al., 2019a; Singh et al., 2017; Vicknasingam et al., 2010).

Kratom has recently gained popularity as an ethnomedicinal remedy in Western countries, especially in the United States (US), where it is sold online and elsewhere (e.g., gas station, specialty shops) in different formulations, such as tablets, supplements, capsules, or powder (Prozialeck et al., 2012; Tavakoli et al., 2016). Several user-based surveys revealed use to self-treat acute/chronic pain, among other psychiatric conditions, including opioid and substance use disorders (Bath et al., 2020; Coe et al., 2019; Garcia-Romeu et al., 2020; Grundmann, 2017). A case report also referred to its successful use in alleviating COVID-19 related pain (Metastasio et al., 2020).

However, despite this increased scientific interest in kratom, the evidence supporting such self-reported claims is still lacking. It is known that its psychoactive effects are mainly dependent on its major metabolite 7-OH-mitragynine (7HMG) and *mitragynine* (MG), which together account for 68% of all the alkaloids present in the plant (Hassan et al., 2013; Kruegel and Grundmann, 2018; Shellard, 1974; Takayama, 2004).

Mitragynine (IUPAC name (E)-2-[2S,3S,12bS)-3-ethyl-8-methoxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]-quinolizin-2-yl]-3-methoxyprop-2-enoate) is an indole alkaloid Corynanthe-type having a monoterpene portion similarly to yohimbine and the psychedelic substance voacangine (Han et al., 2020; Hassan et al., 2013; Kong et al., 2017a; Ramanathan et al., 2015). It is insoluble in both basic and aqueous solutions but possesses a high solubility in typical organic solvents (e.g., acetone, acetic acid, alcohol, chloroform, and diethyl-ether) (Han et al., 2020; Kong et al., 2017a; Ramanathan et al., 2015). It has intermediate lipophilicity and a high capacity to cross the blood-brain barrier (Yusof et al., 2019).

The compound has been described as a G-protein biased atypical opioid (Faouzi et al., 2020; Gutridge et al., 2020; Raffa et al., 2018) that acts as mu- and delta-opioid receptor agonist (Foss et al., 2020; Matsumoto et al., 1996b, 2006), and kappa-opioid receptor antagonist-like, without β-arrestin recruitment (Kruegel et al., 2016; Todd et al., 2020; Váradi et al., 2016). Mitragynine also possesses a non-opioid action through (α2) adrenergic receptors, adenosine (A2A), dopamine (D2), and serotonin (5-HT2A, 5-HT2C, and 5-HT7) receptors (Harun et al., 2015; Hiranita et al., 2019; Matsumoto et al., 1996a, 1996b, 1997).

The contribution of these receptors in the (acclaimed) effects of kratom has yet to be determined. A drawback is that most of the available data has been collected in users. It derives from online surveys, drug fora, and case reports. Additionally, Ramachandram et al. (2019) reported that the association between the pharmacodynamics and -kinetics of mitragynine in (pre)clinical models had not been studied yet.

Limited evidence has shown that the compound possesses a biphasic elimination pattern after both oral (p.o.) (half-life (T1/2):3–9 h) and intravenous (i.v.) (T1/2:13 h) administration in rodents (Kong et al., 2017b; Ya et al., 2019), and a large volume of distribution when it was administered (i.v.) in dogs (Maxwell et al., 2020). On the other side, mitragynine has been shown to follow a two compartmental model after oral intake in a small sample of kratom users, with a T1/2 of 23.24 ± 16.07 h (Trakulsrichai et al., 2015).

The metabolism of mitragynine has been described to be mainly hepatic in both human microsomes (Kamble et al., 2019) and preclinical models (Ya et al., 2019), and it would be mediated by cytochrome P450 (CYP450) (Basiliere and Kerrigan, 2020; Hanapi et al., 2013; Kong et al., 2011), which may also be involved in potential drug-drug interaction.

Serious adverse events, including fatalities (Corkery et al., 2019; Wong and Mun, 2020), have been reported only in Western countries, mainly when kratom is used in recreational settings. Suggested reasons are extreme high dose, and co-administration of benzodiazepines, amphetamines, or ethanol, or the presence of adulterants, like the synthetic O-desmethyl tramadol (Anwar et al., 2016; Corkery et al., 2019; Kronstrand et al., 2011; Olsen et al., 2019). Other serious events have been associated with chronic kratom use (Alsarraf et al., 2019; Anwar et al., 2016; Grundmann, 2017; Schimmel and Dart, 2020) and include the risk of addiction, dependence, and withdrawal (Singh et al., 2018c; Veltri and Grundmann, 2019).

The Food and Drug Administration (FDA) and the US Drug Enforcement Administration (DEA) considered these kratom-related reports as dangerous and consequently proposed to place the plant in Schedule I of the Controlled Substances Act (CSA) in 2016 (Eastlack et al., 2020; Grundmann, 2017; Henningfield et al., 2018). However, since a broad public opposition reversed this action, kratom is still legal at the federal level in the US, with many users claiming its therapeutic potential, in the absence of sufficient clinical evidence.

Given this background, the current systematic review aims to investigate whether kratom has potential medical benefits based on preclinical and clinical studies measuring acute and chronic effects on behavior and other clinical outcomes. The second aim was to investigate possible safety issues in humans. The medical applications of kratom reported by users in traditional and non-traditional settings were used to define this review's search strings.

2 | MATERIALS AND METHODS

2.1 | Data sources and search strategy

A literature search was performed using the PubMed and the Medline database to identify the scientific publications related to kratom's potential therapeutic utility and safety, as investigated in (pre) clinical research. The search, which was carried out between April

and August 2020, consisted of assessing titles and abstracts using both Medical Subject Headings, or subheadings (MeSH) and free-text terms. The choice of search terms was informed by recent high-quality reviews, papers, and online surveys that reported anecdotal data related to kratom's benefits in treating pain, psychiatric symptoms and conditions, and several other medical applications (e.g., hypertension, inflammatory conditions, diabetes).

The query's search strings included a combination of substance [1] and symptoms/condition [2] strings; both included the Boolean command 'OR', and they were combined with 'AND'. The terms used in [1] were kratom, mitragynine, mitragyna, *Mitragyna speciosa*. The terms used in [2] were: ADD, addiction, ADHD, affective disorders, analgesia, analgesic, analgesics, anorexia, anthelmintic, antidepressant, anti-inflammatory, antimalarial, antinociceptive, anxiety, anxiolytic, attention deficit disorder, attention deficit hyperactivity disorder, bipolar disorder, blood pressure, cough, dependence, depression, diabetes, diarrhea, diarrheal disease, fever, gastric, infection, inflammation, mood disorders, "muscle AND relaxation", opioid use disorder, pain, psychosis, psychotic disorders, stress, stress disorders post traumatic, substance-related disorders, treatment-resistant depression, withdrawal. Terms in this string were combined with 'OR'. No period restrictions were applied. This search led to 224 hits and was updated on November 2020, to identify records that could have potentially been published during the preparation of this paper for submission. This search gave 7 additional articles.

2.2 | Inclusion/exclusion criteria

Taking into account the review method and the aim of this study, exclusion criteria were the following: (1) non-original research articles or publications not pertinent or not potentially related to the aims, including those mainly focused on methods of identification in biological samples or sold products, chemistry and physicochemical properties, pharmacology, including pharmacodynamic and pharmacokinetic properties, toxicology or other topics (fatalities, harm reduction, legal status); (2) review, commentaries, or other surveys of the literature; (3) case series and case reports because of their high potential of bias in the study designs; (4) data in humans derived from online surveys.

Studies were included if they met all of the following criteria: (1) preclinical study, in vitro or in vivo, investigating the pharmacology or toxicology potentially related to the review aim, and (2) any clinical outcome providing sufficient scientific evidence of kratom, mitragynine, mitragyna and related or derivative compounds, that would support the traditional medical uses or anecdotal benefits reported by users.

2.3 | Study selection

All procedures were performed according to PRISMA guidelines (Moher et al., 2009). The selection was conducted in two stages: an initial screening of titles and abstracts against the inclusion criteria to identify potentially relevant papers, followed by screening the full papers assessed for eligibility. The selection was discussed in a small team of four (EP, ET, JR, KK).

2.4 | Data extraction

When a record reported a combination of review-relevant and -irrelevant data, only the former was included. Based on the included articles' content, the review was organized in the following categories: (pre)clinical evidence related to potential therapeutic use in pain, withdrawal and dependence, and other medical conditions, and therapeutic application or safety issues in humans.

3 | RESULTS

3.1 | Studies description

In total, 63 studies met the eligibility criteria. After an initial screening, 17 were removed, as they focused on *Mitragyna* genus *per se* or on kratom pharmacology and toxicology data and thus not relevant for this review. Additional studies (29) were included in the analysis as a further assessment of relevant citations emerged. Overall, 75 records were deemed relevant to this systematic review (details of the selection process are shown in Figure 1). These included 18 studies performed in humans, and 57 preclinical studies, that were mainly in vivo studies with a brief observation period, with nine having a more extended observation period (Cheaha et al., 2015; Grewal, 1932b; Harun et al., 2020; Hassan et al., 2020; Khor et al., 2011; Kumarnsit et al., 2006, 2007a; Meepong and Sooksawate, 2019; Wilson et al., 2020), and other nine were in vitro (Abdul Aziz et al., 2012; Fakurazi et al., 2013; Ghazali et al., 2011; Goh et al., 2014; Grewal, 1932b; Jamil et al., 2013; Juanda et al., 2019; Parthasarathy et al., 2009; Yuniarti et al., 2020). Since six preclinical studies gave evidence for two potential therapeutic uses, the related content will be described in each specific section of the results.

3.2 | (Pre)clinical evidence of potential therapeutic use

3.2.1 | Pain

Twenty-three *in vivo* (mice, rats, or dogs) studies provided evidence for kratom's potential therapeutic use in the treatment of acute pain (Carpenter et al., 2016; Criddle, 2015; Fakurazi et al., 2013; Hiranita et al., 2019; Idid et al., 1998; Macko et al., 1972; Matsumoto et al., 1996a, 1996b, 2004, 2005, 2006, 2008; Mossadeq et al., 2009; Reanmongkol et al., 2007; Sabetghadam et al., 2010, 2013; Shamima et al., 2012; Stolt et al., 2014; Takayama et al., 2002; Thongpradichote et al., 1998; Wilson et al., 2020) and chronic pain

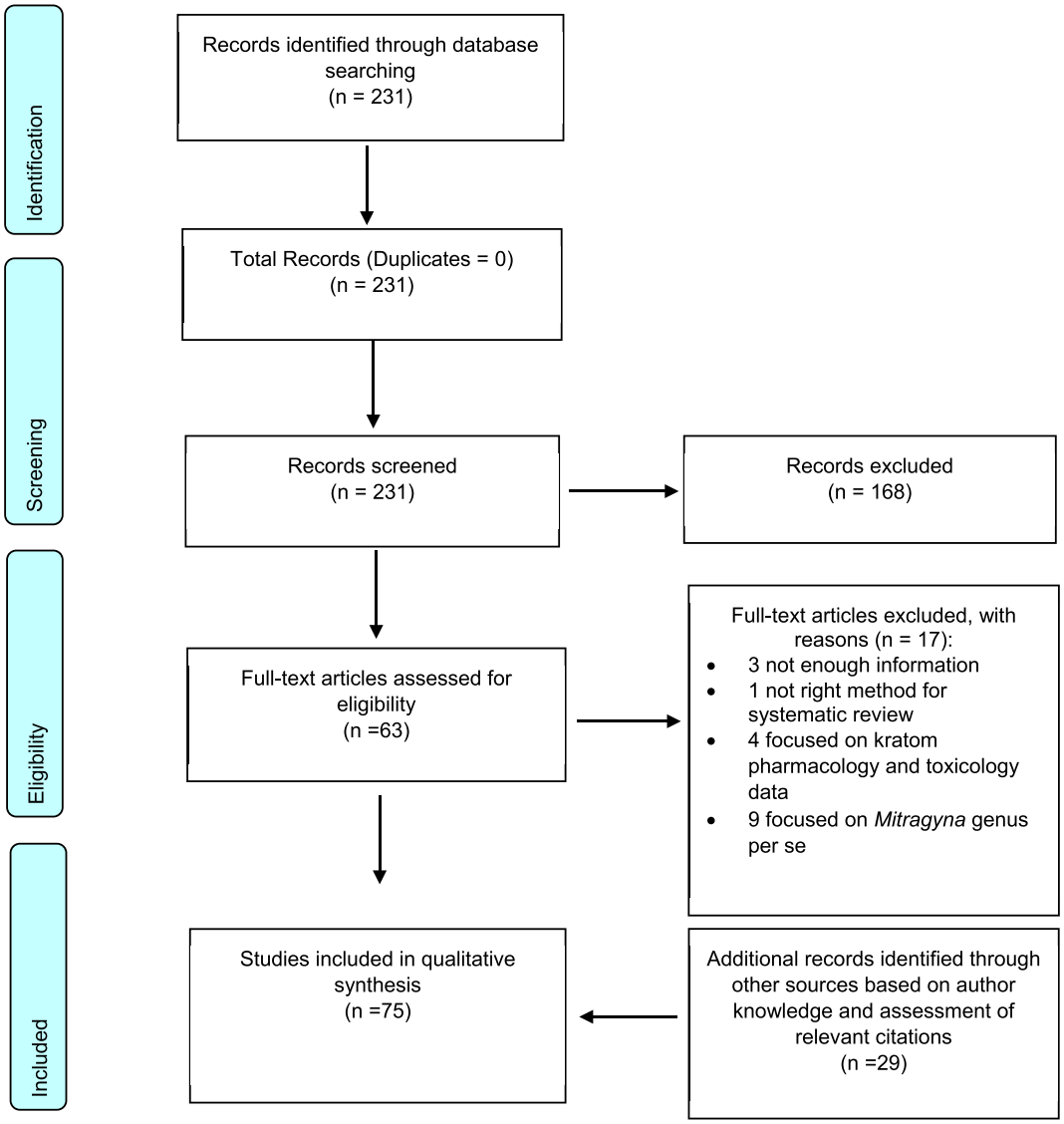

FIGURE 1 PRISMA flowchart depicting the selection and review process that resulted in 75 articles for inclusion in the current review

(Foss et al., 2020; Matsumoto et al., 2014). The antinociceptive effects of the studied preparations were shown in the different models of acute thermal or mechanical stimulus-induced pain, and neuropathic pain, after administration via a range of routes (p.o., i.p., i.v., or i.c.v.).

The studied preparations were *Mitragyna speciosa* (MS) aqueous or methanol or alkaloid extracts (Carpenter et al., 2016; Criddle, 2015; Mossadeq et al., 2009; Reanmongkol et al., 2007; Sabetghadam et al., 2010, 2013), lyophilized kratom tea (LKT) (Wilson et al., 2020), mitragynine alone (Carpenter et al., 2016; Criddle, 2015; Fakurazi et al., 2013; Foss et al., 2020; Hiranita et al., 2019; Idid et al., 1998; Macko et al., 1972; Matsumoto et al., 1996a, 1996b; Shamima et al., 2012; Thongpradichote et al., 1998), or mitragynine + paynantheine (Stolt et al., 2014), and its synthetic derivatives MG Pseudoindoxyl (Takayama et al., 2002) and [(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] (MGM-9) (Matsumoto et al., 2008), or 7HMG (Matsumoto et al., 2004, 2005, 2006), and its derivatives (E)-methyl 2-((2S,3S,7aS,12aR,12bS)-3-ethyl-7a-hydroxy-8-methoxy-1,2,3,4,6,7,7a,12,12a,12b-decahydroindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate (MGM-15) and (E)-methyl 2-((2S,3S,7aS,12aR,12bS)-3-ethyl-9-fluoro-7a-hydroxy-8-methoxy-1,2,3,4,6,7,7a,12,12a,12b-decahydroindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate (MGM-16) (Matsumoto et al., 2014).

According to the evidence included in our analysis, mitragynine's analgesic effect was similar to classical opioids oxycodone and morphine (MOR) (Carpenter et al., 2016; Criddle, 2015). When combined with MOR in long-term treatment, the analgesic effect was more pronounced (Fakurazi et al., 2013). Further, it was described as more potent and relatively safer than the MS alkaloid extract (Sabetghadam et al., 2013). Wilson et al. (2020) also found LKT's analgesic effect similar to MOR, with relatively fewer negative effects (Wilson et al., 2020). 7HMG, a partial mu- and delta-

opioid receptors agonist, was described as more potent than MOR (Matsumoto et al., 2004, 2006), with a minor intestinal transit inhibition (Matsumoto et al., 2006). However, it was also found responsible for a locomotor activity increase in a dose-dependent manner (Matsumoto et al., 2008) and producing cross-tolerance to MOR (Matsumoto et al., 2005, 2008). Among its derivatives, authors found MGM-16 to have a superior potency as an opioid agonist in comparison to both MGM-15 and 7HMG (Foss et al., 2020; Matsumoto et al., 2014), and Matsumoto et al. (2008) reported MGM-9 to have higher potency, with lower adverse effects, whether compared to MOR and 7HMG (Matsumoto et al., 2008).

Further, four studies (Fakurazi et al., 2013; Macko et al., 1972; Mossadeq et al., 2009; Wilson et al., 2020) showed that kratom also exerts other therapeutic effects besides analgesic properties, including applications in opioid withdrawal, described in more detail below.

3.2.2 | Withdrawal and dependence

Twelve *in vivo* studies (mice, rats or zebrafish) and two *in vitro* studies provided evidence for kratom so potential therapeutic use in the treatment of both opioid (Cheaha et al., 2017; Fakurazi et al., 2013; Harun et al., 2020; Hassan et al., 2020; Hemby et al., 2019; Jamil et al., 2013; Khor et al., 2011; Meepong and Sooksawate, 2019; Wilson et al., 2020; Yue et al., 2018) and alcohol use disorders (Cheaha et al., 2015; Gutridge et al., 2020; Kumarnsit et al., 2007a; Vijeepallam et al., 2019), as shown by the effects of the studied preparations (kratom extracts, LKT, mitragynine and other alkaloids; p.o. or i.p. or i.v. or intragastrically) in models of induced withdrawal, drug consumption/replacement, and dependence.

Among the extracts, the MS alkaloid (Cheaha et al., 2015) and aqueous extract (Kumarnsit et al., 2007a) attenuated ethanol withdrawal. The methanol extract was found to reduce the ethanol-seeking behavior (Vijeepallam et al., 2019), and both extracts (with or without 7HMG) and alkaloids (e.g., paynantheine, speciogynine, mitragynine, 7HMG) diminished alcohol intake (Gutridge et al., 2020). LKT (Wilson et al., 2020) and mitragynine were reported to lessen morphine withdrawal (Cheaha et al., 2017; Harun et al., 2020; Khor et al., 2011), with Hassan et al. (2020) suggesting that this mitragynine effect may resemble that produced by methadone and buprenorphine (Hassan et al., 2020). Additionally, mitragynine attenuated morphine dependence as well (Hemby et al., 2019; Jamil et al., 2013; Meepong and Sooksawate, 2019), and Yue et al. (2018) demonstrated a reduction by the compound of response rates in the model of heroin-induced Conditioned Place Preference (CPP) (Yue et al., 2018). Further, Fakurazi et al. (2013) found that mitragynine possesses the potential to reduce morphine tolerance in a chronic morphine administration model, defined by transcription factor cAMP response element binding (CREB)'s activation and the consequent increase in cAMP level's expression (Fakurazi et al., 2013).

3.2.3 | Other medical conditions

Twenty-two (15 *in vivo* in mice, rats or frogs, rabbits and cats, 7 *in vitro*) studies, plus four previously described to report also effects in pain (Macko et al., 1972; Mossadeq et al., 2009) and withdrawal or dependence (Khor et al., 2011; Kumarnsit et al., 2007a), provided evidence for kratom's potential therapeutic use in the treatment of some conditions.

Both mitragynine and MS extracts (p.o. or i.p.) were found to produce several effects including gastroprotective action (Chittrakarn et al., 2018), inhibition of acid gastric secretion (Tsuchiya et al., 2002), and anti-inflammatory (Aziddin et al., 2005; Chittrakarn et al., 2018; Macko et al., 1972; Mossadeq et al., 2009), stress mitigating (Hazim et al., 2011; Khor et al., 2011; Vázquez López et al., 2017), anxiolytic-like (Hazim et al., 2014; Khor et al., 2011; Moklas et al., 2013) and antidepressant-like effects (Idayu et al., 2011; Kumarnsit et al., 2007a, 2007b), anorectic action (Chittrakarn et al., 2008; Grewal, 1932b; Kumarnsit et al., 2006, 2007b), antimutagen/anticancer (Ghazali et al., 2011; Goh et al., 2014), antioxidant (Goh et al., 2014; Grewal, 1932b; Parthasarathy et al., 2009; Yuniarti et al., 2020), and muscle relaxant effect (Chittrakarn et al., 2010). The extract had a more significant action in terms of muscle relaxation when compared to mitragynine (Chittrakarn et al., 2010).

Further, only mitragynine was found to have also dose-dependent anthelmintic activity (Abdul Aziz et al., 2012), antitussive (Macko et al., 1972), paramoecia killing action, anti-hypertensive, and anesthetic effects (Grewal, 1932b), while MS extracts showed to exert antibacterial (Juanda et al., 2019; Parthasarathy et al., 2009), bodyweight decreasing and dose-dependent antidiarrheal (Chittrakarn et al., 2008), antipsychotic-like (Vijeepallam et al., 2016), antipyretic effects (Salleh et al., 2011) and facilitation of learning (Senik et al., 2012).

For a complete overview, see Table 1.

3.2.4 | Therapeutic application and safety issues in humans

Among the 18 clinical studies, three were experimental studies, with respectively an interventional, a prospective, and a randomized placebo-controlled, double-blind design. 15 were observational with a cross-sectional ($N = 13$) and a retrospective ($N = 2$) design. All these clinical studies were performed in Southern East Asia, and participants were kratom users.

Among the observational studies (Leong Bin Abdullah et al., 2019a, 2019b, 2020a, 2020b; Saref et al., 2019a, 2019b; Singh et al., 2014, 2015, 2018a, 2018b, 2018c, 2018d, 2019a, 2019b, 2019c), none reported evidence of therapeutic application. Safety issues related to chronic kratom use were shown in nine of these studies. Issues reported were high cholesterol level (Leong Bin Abdullah et al., 2020a), a slight increase in both HDL and LDL (cholesterol) values (Singh et al., 2018a), visual episodic memory or

TABLE 1 Preclinical studies

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Antinociceptive Effects							
Carpenter et al. (2016)	Comparison on thermal nociception between MS articles and opioid agonists	MG (30 mg/kg, i.p.) MSE (300 mg/kg, i.p.) MS alkaloids fraction (75 mg/kg, i.p.)	MOR (10 mg/kg, i.p.) Oxycodone (3 mg/kg, i.p.)	N/Y	Sprague Dawley rats, 6 (9–10)	Acute thermal pain	HPT/Increase in latencies to perform an antinociceptive response
		MG (100 mg/kg, p.o.) MSE (300 mg/kg, p.o.)	Oxycodone (6 mg/kg, p.o.)	//	Sprague Dawley rats, 4 (8–9)	//	//
Criddle (2015)	Comparison between MS articles and opioid agonists	MG (30 mg/kg, i.p.) MSE (300 mg/kg, i.p.) MS alkaloids fraction (75 mg/kg, i.p.)	MOR (10 mg/kg, i.p.) Oxycodone (3 mg/kg, i.p.)	N/Y	Sprague-Dawley rats, 6 (10)	Acute thermal pain	HPT/Increase in latencies to perform an antinociceptive response
		MG (100 mg/kg, p.o.) MSE (300 mg/kg, p.o.)	Oxycodone (6 mg/kg, p.o.)	//	Sprague Dawley rats, 4 (8–10)	//	//
Fakurazi et al. (2013)[a]	Enhancement of MG's analgesic action in combination with MOR	MG (15, 25 mg/kg, i.p.) MOR + MG (5 mg/kg + 15, 25 mg/kg, i.p.)	MOR (5 mg/kg, i.p.)	Y/N	ICR mice, 6 (7)	Acute thermal pain	HPT/Increase in latencies to perform an antinociceptive response
Foss et al. (2020)	Effect on neuropathic pain	MG (1, 5, 10 mg/kg, i.p.)	ND (ND)	N/Y	Male Sprague-Dawley rats, 4 (7–8)	Allodynia oxaliplatin (6 mg/kg i.p.) induced; locomotor activity	Mechanical sensitivity test/ Reduction of paw withdrawal threshold; % of ambulatory counts in the VEH (0)
		MG (30 mg/kg, i.p.)	ND (ND)	//	Male Sprague-Dawley rats, 2 (7)	//	% of ambulatory counts in the VEH (–)
Hiranita et al. (2019)	Effect on schedule-controlled responding and antinociception	MG (3.2, 5.6, 10, 17.8, 32, 56 mg/kg, i.p.)	ND (ND)	N/Y	Sprague-Dawley rats, 2 (16)	Operant procedures for food reinforcement; acute thermal pain	Multiple cycles fixed ratio 10 schedules of food delivery/ Reduction of schedule-controlled responding; HPT/Increase in latencies to perform an antinociceptive response (like MOR)
		MG + MOR (3.2, 5.6, 10, 17.8, 32, 56 mg/kg + 3.2, 5.6, 10, 17.8, 32, 56 mg/kg, i.p.)	ND (ND)	//	//	//	Multiple cycle fixed ratio 10 schedule of food delivery (0), HPT (0) (MG 17.8 mg)

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Antinociceptive Effects							
Idid et al. (1998)	Comparison of antinociceptive effect between MG, paracetamol and MOR	MG (200 mg/kg, p.o.)	MOR (5 mg/kg, p.o.) paracetamol (100 mg/kg, p.o.)	N/Y	Albino mice, 4 (6)	Pain; acute thermal pain	Acetic acid-induced writhing test/Inhibition of writhing constrictions; HPT, cold TFT/Increase in latencies to perform an antinociceptive response
Macko et al. (1972)[a]	MG pharmacology	MG (92 mg/kg, p.o.)	ND (ND)	ND/ND	Mice, ND	Acute thermal pain	HPT/Increase in latencies to perform an antinociceptive response
		MG (92 mg/kg, s.c.)	//	//	//	//	//
		MG (ND, s.c.)	//	//	Rat, ND	//	TFT/Increase in latencies to perform an antinociceptive response
		MG (ND, i.p.)	//	//	//	//	//
		MG (ND, p.o.)	//	//	//	//	//
		MG (ND, p.o.)	//	//	Dogs, ND	//	Hindleg flick/Antinociceptive response
Matsumoto et al. (1996a)	Roles of central monoaminergic systems in the antinociceptive action	MG (1, 3, 10 mg, i.c.v.)	MOR (0.3, 1, 3 mg/mouse, i.c.v.)	N/Y	ddY mice, 2 (40)	Acute thermal pain	TPT, HPT/Increase in latencies to perform an antinociceptive response
Matsumoto et al. (1996b)	Antinociceptive effect	MG (3, 10, 30 mg/kg, i.p.)	ND (ND)	N/Y	ddY mice, 4 (10)	Acute thermal pain	TFT, HPT/Increase in latencies to perform an antinociceptive response
		MG (1, 3, 10 mg/mouse, i.c.v.)	//	//	//	//	//
Matsumoto et al. (2004)	Opioid effects	7HMG (2.5, 5, 10 mg/kg, s.c. or p.o.)	MOR (2.5, 5, 10 mg/kg, s.c.) or MOR (20 mg/kg, p.o.)	N/Y	ddY mice, 3 (6)	Acute thermal pain	TFT/Increase in latencies to perform an antinociceptive response
		7HMG (5, 10, 20 mg/kg, s.c. or p.o.)	MOR (5, 10, 20 mg/kg, s.c.) or MOR (20 mg/kg, p.o.)	//	//	//	HPT/Increase in latencies to perform an antinociceptive response
Matsumoto et al. (2005)	Antinociceptive and opioid effects	7HMG (2.5, 5, 10 mg/kg, s.c.)	ND	N/Y	ddY mice, 4 (6)	Acute thermal pain	TFT/Increase in latencies to perform an antinociceptive response

(Continues)

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Antinociceptive Effects							
Matsumoto et al. (2006)	Mechanism of antinociception and comparison with MOR	7HMG (0.25, 0.5, 1.0, 2.0 mg/kg, s.c.) or MOR (1.25, 2.5, 5, 8 mg/kg, s.c.)	ND (ND)	Y/Y	ddY-strain mice, 5 (7–8)	Acute thermal pain	TFT, HPT/Increase in latencies to perform an antinociceptive response
Matsumoto et al. (2008)	MG derivative compounds' effects	MGM-9 (0.25, 0.5, 1, 2 mg/kg, s.c.)	MOR (1.25, 2.5, 5, 8 mg/kg, s.c.) 7HMG (0.25, 0.5, 1, 2 mg/kg, s.c.)	Y/Y	ddY-strain mice, 5 (7–9)	Acute thermal pain	TFT, HPT/Increase in latencies to perform an antinociceptive response
		MGM-9 (1, 2, 4, 8 mg/kg, p.o.)	MOR (25, 50, 100 mg/kg, p.o.) 7HMG (1, 2, 4 mg/kg, p.o.)	//	//	//	//
		MGM-9 (0.025, 0.05, 0.1, 0.2 mg/kg, s.c.)	MOR (0.25, 0.5, 1 mg/kg, s.c.) 7HMG (0.05, 0.1,0.2, 0.4 mg/kg, s.c.)	//	//	Pain	Writhing test/Reduction of number of writhing responses
		MGM-9 (0.25, 0.5, 1, 2 mg/kg, s.c.)	MOR (2.5, 5, 10 mg/kg, p.o.) 7HMG (0.5, 1, 2, 4 mg/kg, p.o.)	//	//	//	//
Matsumoto et al. (2014)	7HMG derivatives' potential effect on acute/chronic pain	MGM-15 (0.125, 0.25, 0.5, 1 mg/kg, s.c.) or (0.5, 1, 2, 4 mg/kg, p.o.)	ND (ND)	N/Y	ddY-strain mice, 5 (8)	Acute thermal pain	TFT/Increase in latencies to perform an antinociceptive response
		MGM-16 (0.025, 0.05, 0.1, 0.2 mg/kg, s.c.) or (0.125, 0.25, 0.5, 1 mg/kg, p.o.)	ND (ND)	//	//	//	//
		MGM-16 (0.1, 0.2, 0.4 mg/kg, s.c.)	ND (ND)	Y/Y	ddY-strain mice, 5 (6–7)	Neuropathic pain	Sciatic nerve ligation induced thermal/mechanical hyperalgesia/Increase in paw withdrawal threshold
		MGM-16 (0.5, 1, 2 mg/kg, p.o.)	Gabapentin (100 mg/kg, p.o.)	//	ddY-strain mice, 6 (6–7)	//	–

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Antinociceptive Effects							
Mossadeq et al. (2009)[a]	Antinociceptive activity	MS ME (50, 100, 200 mg/kg, i.p.)	ASA (100 mg/kg, i.p.) MOR (5 mg/kg, i.p.)	Y/N	Sprague-Dawley rats, 6 (10)	Pain	Formalin test/Inhibition of time spent in antinociceptive response
		MS ME (50, 100, 200 mg/kg, i.p.)	ASA (100 mg/kg, i.p.) MOR (5 mg/kg, i.p.)	//	Balb C mice, 6 (10)	Acute thermal and mechanical pain	HPT/Increase in latencies to perform an antinociceptive response; acetic acid-induced writhing test/Inhibition of writhing constrictions
Reanmongkol et al. (2007)	Effects on analgesic and behavioral activities	MS ME (50, 100, 200 mg/kg, p.o.) or MS Alk-E (5, 10, 20 mg/kg, p.o.)	MOR (10 mg/kg, p.o.)	N/Y	Swiss mice, 5 (10)	Acute thermal pain	HPT/Increase in latencies to perform an antinociceptive response
		MS ME (50, 100, 200 mg/kg, p.o.) or MS Alk-E (5, 10, 20 mg/kg, p.o.)	MOR (10 mg/kg, p.o.)	//	Wistar rats, 5 (6)	//	TFT (0)
		MS ME (50, 100, 200 mg/kg, p.o.) or MS Alk-E (5, 10, 20 mg/kg, p.o.)	Methamphetamine (1 mg/kg, i.p.)	//	Swiss mice, 5 (10)	ND	Locomotor activity (0)
		MS ME (50, 100, 200 mg/kg, p.o.) or MS Alk-E (5, 10, 20 mg/kg, p.o.)	ND (ND)	//	Swiss mice, 4 (10)	Pentobarbital-induced sleep	Sleeping time (0)
Sabetghadam et al. (2010)	Antinociceptive activity	MS Alk-E (5, 10, 20 mg/kg, p.o.) MS ME (50, 100, 200 mg/kg, p.o.) MS AE (100, 200, 400 mg/kg, p.o.)	MOR (5 mg/kg, s.c.) Aspirin (300 mg/kg, p.o.)	Y/Y	Sprague-Dawley rats, 6 (5)	Acute thermal pain	HPT, TFT/Increase in latencies to perform an antinociceptive response
Sabetghadam et al. (2013)	Dose-response relationship, safety, and therapeutic indices	MS Alk-E (50, 160, 320, 400 mg/kg, p.o.)	MOR (2.5, 5, 10 mg/kg, s.c.)	N/Y	Swiss albino mice, 3 (6)	Acute thermal pain	HPT/Increase in latencies to perform an antinociceptive response
		MG (4.2, 10.5, 33.6, 67.2, 84 mg/kg, p.o.)	MOR (2.5, 5, 10 mg/kg, s.c.)	//	//	//	//
Shamima et al. (2012)	Investigation on antinociceptive effect	MG (3, 10, 15, 30, 35 mg/kg, i.p.)	MOR (3 mg/kg, i.p.)	Y/N	ICR mice, 7 (8)	Acute thermal pain	HPT/Increase in latencies to perform an antinociceptive response

(Continues)

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Antinociceptive Effects							
Stolt et al. (2014)	Effects on analgesia and behavior	MG + paynantheine (0.5 + 0.025 mg/kg, p.o.) MG + paynantheine (2 + 0.1 mg/kg, p.o.) MG + paynantheine (4 mg/kg + 0.2 mg/kg, p.o.)	ND (ND)	N/Y	WT mice and mu-opioid receptor KO mice, 8 (8–15)	Locomotor activity	Locomotor activity recording/Reduced time spent in (horizontal + vertical) activity
		MG + paynantheine (2 + 0.1 mg/kg, i.p.) MG + paynantheine (4 mg/kg + 0.2 mg/kg, i.p.)	//	//	WT mice and mu-opioid receptor KO mice, 6 (8–15)	Locomotor activity; anxiety; acute thermal pain	Locomotor activity recording/Reduced time spent in (horizontal + vertical) activity; EPM test/Reduced time spent on open arms; HPT (0)
		MG + paynantheine (10 mg/mouse + 0.5 mg/mouse, i.c.v.) MG + paynantheine (20 mg/mouse + 1 mg/mouse, i.c.v)	//	//	//	//	Locomotor activity recording/Reduced time spent in (horizontal + vertical) activity; EPM test (ND); HPT/Increase in latencies to perform an antinociceptive response
		MG + paynantheine (2 + 0.1 mg/kg, p.o.) MG + paynantheine (4 mg/kg + 0.2 mg/kg, p.o.)	//	//	//	Anxiety; acute thermal pain	EPM test (0); HPT (0)
Takayama et al. (2002)	Synthesis and opioid agonistic activities	MG (ND, 75 nmol/mouse, i.c.v.) MG Pseudoindoxyl (ND, 12 nmol/mouse, i.c.v.)	MOR (ND, 9 nmol/mouse, i.c.v.)	N/Y	Mice, 4 (9–12)	Acute thermal pain	TFT/Increase in latencies to perform an antinociceptive response
Thongpradichote et al. (1998)	Opioid receptor subtypes involved in the antinociceptive action	MG + antagonists (10 mg, i.c.v.)	MOR (3 mg, i.c.v.)	N/Y	ddY mice, 3 (7–9)	Acute thermal pain	TPT, HPT/Increase in latencies to perform an antinociceptive response
Wilson et al. (2020)[a]	LKT's antinociception and liabilities	LKT (45, 200, 1000, 2000, 4000 mg/kg, p.o.)	MOR (1, 3, 10, 60 mg/kg, i.p. or p.o.)	Y/N	C57BL/6J mice, 5 (8)	Acute thermal pain	55°C warm-water tail-withdrawal assay/Increase in latency to remove the tail

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Withdrawal and dependence							
Cheaha et al. (2015)	Effect on EW-induced physical and cortical hyperexcitabilities	MS Alk-E (60 mg/kg, intragastrically)	Fluoxetine (10 mg/kg, intragastrically)	N/Y	Wistar rats, 3 (8–9)	ND	EEG and EMG signal acquisition (0)
		MS Alk-E (60 mg/kg, intragastrically)	Fluoxetine (10 mg/kg, intragastrically)	//	(ED) Wistar rats, 3 (6-7); (not EW) Wistar rats, 1(6-7); (not ED) Wistar rats, 1 (6-7)	EW	(Withdrawal induced) gamma activity in frontal and parietal cortex and locomotor activity/ Attenuation
Cheaha et al. (2017)	Effect on NAL-precipitated MOR withdrawal and neural signalling in the nucleus accumbens	MG (30, 90, 120 mg/kg, p.o.)	MS Alk-E (20, 40, 60, 80, 100 mg/kg, p.o.)	Y/N	(MOR dependent) Swiss albino ICR mice, 9 (10-12)	NAL-precipitated MOR withdrawal	Jumping behavior and dry-wet fecal excretions/Reduction only with MS Alk-E
		MS Alk-E (80 mg/kg, p.o.)	MOR (15 mg/kg, i.p.)	//	(MOR dependent) Swiss albino ICR mice, 3 (6–8)	ND; locomotor activity	LFP in nucleus accumbens (0); Spontaneous motor activity (0)
Fakurazi et al. (2013)[a]	Effect of the combination on MOR tolerance	MG (15, 25 mg/kg, i.p.)	MOR (5 mg/kg, i.p.) MOR + MG (5 mg/kg + 15, 25 mg/kg, i.p.)	Y/N	ICR mice, 6 (7)	Tolerance and dependence	cAMP/CREB level in thalamus and cortex immunoblotting analysis/Down-regulation with MG + MOR
Gutridge et al. (2020)	Potential reduction of alcohol intake	MSE with 7HMG (10, 30 mg/kg^{-1}, i.p.)	ND (ND)	Y/N	C57BL/6 mice, 2 (8–12)	Moderate- binge alcohol consumption	Level of alcohol intake in two-bottle choice and intermittent, limited access paradigm/ Decrease
		MSE without 7HMG (10, 30 mg/kg^{-1}, i.p.) or paynantheine (10, 30 mg/kg^{-1}, i.p.) or speciogynine (10, 30 mg/kg^{-1}, i.p.) or MG (10, 30, 100 mg/kg^{-1}, i.p.) or 7HMG (1, 3, 10 mg/kg^{-1}, i.p.)	ND (ND)	//	C57BL/6 mice, 2 (8–12)	Locomotor activity	Locomotion assessment/ Reduction with extracts, +/− with other compounds

(Continues)

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Withdrawal and dependence							
Harun et al. (2020)	Potential therapeutic effect on MOR-dependence	MG (1, 10, 30 mg/kg, i.p.)	Buprenorphine (0.1, 0.3, 1.0 mg/kg, i.p.)	N/Y	(MOR dependent) Sprague-Dawley rats, 3 (12)	NAL-precipitated MOR withdrawal	Food-maintained operant responding/ Attenuation of withdrawal, buprenorphine was necessary
Hassan et al. (2020)	Effect on MOR withdrawal	MG (5, 10, 15, 30 mg/kg, i.p.)	ND (ND)	N/Y	(MOR dependent) Sprague-Dawley rats, 5 (6); Sprague-Dawley rats, 1 (6)	Drug replacement treatment in MOR withdrawal	MOR withdrawal behaviors/Attenuation as methadone and buprenorphine
Hemby et al. (2019)	Abuse liability and therapeutic potential	MG (25, 50, 100, 150 µg/inf, i.v.)	ND (ND)	Y/N	Fischer 344 rats, 5 (8-9)	Human drug consumption	Substitution of MOR following MOR self-administration paradigm (0); Re-assessment of MOR self-administration/ Reduction
		7HMG (2.5, 5, 10, 20 µg/inf, i.v.)	ND (ND)	//	Fischer 344 rats, 5 (8-9)	//	Substitution of MOR following MOR self-administration paradigm/ Substitution; Re-assessment of MOR self-administration/ Increase
Jamil et al. (2013)	Effect on cAMP and mu-opioid receptor mRNA expression following chronic MOR treatment	MG (0.1,1, 10, 50 µM, replacing the growth media in the cell culture)	MOR (0.1, 1, 10, 100 µM, replacing the growth media in the cell culture)	ND/ND	Human neuroblastoma SK–N–SH cell, ND	Tolerance and dependence	cAMP level upon forskolin stimulation/Reduction in the brief term, long term (–); mu-opioid receptor mRNA expression (0)
		MG + MOR co- and pre-treatment (0.1,1, 10, 50 µM + 50 µM, replacing the growth media in the cell culture)	NAL (50 µM, replacing the growth media in the cell culture) Methadone (50 µM, replacing the growth media in the cell culture)	//	//	//	cAMP level upon forskolin stimulation in MOR co-treatment/ Reduction; mu-opioid receptor mRNA expression/Down-regulation reduction

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Withdrawal and dependence							
Khor et al. (2011)[a]	Effect on anxiety behavior, cortisol level and expression of stress pathway-related genes in MOR withdrawal	MG (2 mg/L, exposure in water)	MOR (1.5 mg/L, exposure to water) MOR withdrawal (ND, exposure to water)	Y/N	WT zebrafish, 4 (20–25)	Stress-related anxiogenic behaviors in MOR withdrawal; MOR withdrawal-induced stress genes	Novel tank diving tests/ Attenuation; Real-time PCR mRNA expression analysis/ Reduction of genes expression
		MG (1, 2 mg/L, exposure in water)	ND (ND)	//	WT zebrafish, 3 (20-21)	Anxiogenic behaviors in MOR withdrawal	Novel tank diving tests/ Attenuation
		MG (1, 2 mg/L, exposure in water)	MOR (1.5 mg/L, exposure in water) MOR withdrawal (ND, exposure in water)	//	WT zebrafish, 5 (14–23)	MOR withdrawal-induced high cortisol level	Whole-body cortisol assay/Reduction
Kumarnsit et al. (2007a)[a]	Effect on EW	MS AE (100, 300, 500 mg/kg, p.o.)	ND (ND)	N/Y	Swiss albino mice, 4 (10)	Locomotor activity	Spontaneous motor activity (0)
		MS AE (300 mg/kg, p.o.)	Not EW	//	(ED) Swiss albino mice, 3 (10)	EW	EW induced behaviors/ Reduction
Meepong and Sooksawate (2019)	Abuse liability and potential in the treatment of opioid addiction	MG + Sal (5, 10 mg/kg + ND, i.p.) Sal + VEH (ND, i.p.)	MG + MOR (5, 10 mg/kg + 5 mg/kg, i.p.) Sal + MOR (ND + 5 mg/kg, i.p.)	Y/N	Wistar rats, 5 (6–9)	Abuse liability	Acquisition of MOR-induced CPP/ Suppression
		MOR or Sa l + MG (5 mg/kg or ND +5, 10 mg/kg, i.p.) Sal + MG (ND + 5, 10 mg/kg, i.p.)	MOR + Sal (5 mg/kg + ND i.p.) Sal + Sal (ND, i.p.)	//	Wistar rats, 4 (6–9)	//	Expression of MOR-induced CPP/ Attenuation
		(Chronic MOR) MG + NAL (10, 30 mg/kg + 3 mg/kg, i.p.)	(Chronic Sal) Sal + NAL (ND + 3 mg/kg, i.p.)	//	ICR mice, 4 (6–8)	NAL-induced chronic MOR withdrawal	Jumping behavior, Straub tail reaction/ Reduction
Vijeepallam et al. (2019)	Effect on ethanol-seeking behavior	MS ME (50, 75, 100 mg/kg, p.o.)	Acamprosate (300 mg/kg, p.o.) Clozapine (1 mg/kg, p.o.)	Y/Y	Swiss albino mice, 7 (4)	Ethanol-induced CPP	Ethanol-place preference/ Reversed effect
		MS ME (50, 75, 100 mg/kg, p.o.) MS ME + Sal or VEH (100 mg/kg + ND, p.o.)	Acamprosate (300 mg/kg, p.o.) Clozapine (1 mg/kg, p.o.) Sal + VEH (ND, ND)	//	Swiss albino mice, 8 (10–11)	Drug self-administration	Difference between pre- and post-conditioning with ethanol/ Reduction of the runtime to reach goal box, prolonged runtime in ethanol-conditioned

(Continues)

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Withdrawal and dependence							
Wilson et al. (2020)[a]	LKT's therapeutic potential to prevent NAL-precipitate MOR WD	LKT escalating doses (30, 35, 45, 60, 100, 125 mg/kg, p.o.) + LKT (25 mg/kg, p.o.) 7 days MOR (10, 15, 20, 30, 50, 60, 70, 75, 80 mg/kg, i.p.) + LKT (40 mg/kg, p.o.) 4 days MOR (10, 15, 20, 30, 50, 60, 70, 75, i.p.) + LKT continuing (100 mg/kg) + LKT (40 mg/kg, p.o.) 4 days MOR (10, 15, 20, 30, 50, 60, 70, 75, i.p.) + LKT taper (100, 80, 70, 60, 50 mg/kg, p.o.) + LKT (40 mg/kg, p.o.)	MOR escalating doses (10, 15, 20, 30, 50, 60, 70, 75 mg/kg, i.p.) + MOR (25 mg/kg, i.p.)	Y/N	Mice, 6 (8–10)	NAL-precipitated MOR withdrawal	Opioid withdrawal behaviors/Attenuation
Yue et al. (2018)	Abuse liability	MG (0.1, 0.3, 1, 3 mg/kg, i.v.)	Heroine (0.001, 0.003, 0.01, 0.03 mg/kg/inj, i.v.) Methamphetamine (0.002, 0.007, 0.022, 0.068 mg/kg/inj, i.v.)	Y/N	Sprague-Dawley rats (trained to self-administer methamphetamine), ND (6)	Methamphetamine induced CPP	Response rates (0)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Other effects							
Abdul Aziz et al. (2012)	Anthelmintic properties	MG (0.2, 0.4, ND mg/mL, ND)	ND (ND)	ND	L3 stage larvae of strongyles, ND	ND	Observation/Absence of motility - mortality
Aziddin et al. (2005)	Anti-inflammatory properties	MS Alk-E (50 mg/kg, i.p.)	ASA (20 mg/kg, i.p.)	N/Y	Sprague Dawley rats, 3(6)	Acute inflammation	Carrageenin-induced paw edema/Inhibition

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Other effects							
Chittrakarn et al. (2008)	Effect on the gastrointestinal tract	MS ME (50, 100, 200, 400 mg/kg, p.o.)	Loperamide (6 mg/kg, p.o.)	N/Y	Wistar rats, 6 (10)	Castor oil-induced diarrhea	Fecal matter and change in bodyweight/Reduction; intestinal transit and intestinal fluid/Inhibition
		MS ME (100, 200, 400 mg/kg, p.o.) MS ME + NAL (100, 200, 400 mg/kg + 5 mg/kg, p.o.)	NAL (5 mg/kg, i.p.)	//	Wistar rats, 8 (10)	//	Defecation frequency, total score, fecal weight (0); Change in bodyweight (0)
		MS ME (100, 200, 400 mg/kg, p.o.)	MOR (3 mg/kg, i.p.)	//	Wistar rats, 18 (10)	ND	Bodyweight daily recording/ Reduction; CCK blood levels from the orbital plexus (0); intestinal transit and intestinal fluid (0)
Chittrakarn et al. (2010)	Effect on neuromuscular junction	MG (0.0156 mg/ml, addition to the preparation) MS ME (0.1, 0.25, 0.5, 1 mg/ml, addition to the preparation)	ND (ND)	N/N	Wistar rats' isolated phrenic nerve and hemidiaphragm preparation, 5 (8)	ND	Recording of neurally evoked twitch/Decrease; Recording of direct muscle twitch/ Decrease
		MS ME (0.1, 0.25, 0.5, 1 mg/ml, addition to the preparation) + positive controls	Pancuronium (0.6 mmol, addition to the preparation) Succinylcholine (1.3 mmol, addition to the preparation)	//	//	//	–
		MG (2 mg/ml, addition to the preparation) MS ME (10, 20, 40 mg/ml, addition to the preparation)	Xilocaine (0.10%, addition to the preparation)	N/N	Wistar rat's isolated sciatic nerve preparation, 6 (6)	//	Recording of compound action potential/Block

(Continues)

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Other effects							
Chittrakarn et al. (2018)	Effect on the peptic ulcer and reflux esophagitis	MS ME (200, 400 mg/kg, p.o.)	MG (2 mg/kg, p.o.) Ranitidine (50 mg/kg, p.o.)	N/Y	Wistar rats, 5(8)	WIR stress induced peptic ulcer	Total gastric acid, gastric content pH, ulcer index, histopathological examination/Reduction of ulcer index, moderate regeneration of ulcerous lesions
		MS ME (200, 400 mg/kg, p.o.)	Omeprazole (20 mg/kg, p.o.)	//	Wistar rats, 4 (8)	ASA treatment- or ET-induced peptic ulcer	//; only moderate regeneration of ulcerous lesions in ET model
		MS ME (200, 400 mg/kg, p.o.)	Sucralfate (500 mg/kg, p.o.)	//	//	Reflux esophagitis	//
Ghazali et al. (2011)	Potential (anti) mutagenic activity	MS AE (3.125, 12.5, 50 mg/ml, addition to bacterial culture)	2-NF or 2-AA (0.1 ml, addition to bacterial culture)	Y/Y	Salmonella typhimurium strain TA 98 cell, 2-5 x 10^8 cells/ml	2-NF, NaN3 and 2-AA induced mutagenicity	Ames (Antimutagenicity) test/ + S9 metabolic activator (+); without (0)
		MS AE (3.125, 12.5, 50 mg/ml, addition to bacterial culture)	NaN3 or 2-AA (0.1 ml, addition to bacterial culture	//	Salmonella typhimurium strain TA 100 cell, 2-5 x 10^8 cells/ml	//	–
Goh et al. (2014)	Antioxidant value and anticancer functions	MG (6.2, 12.5, 25, 50, 100, 200 mM, addition to the cell culture)	SRM (6.2, 12.5, 25, 50, 100, 200 mM, addition to the solution) BA (//) 5-FU (//)	N/Y	Cancer- normal cell lines, 96 well µtitre plates	ND	MTT cell antiproliferation assay/Cytotoxicity
		MG (0.032, 0,0625, 0.125, 0.25, 0.5, 1 mg/ml, addition to the cell culture)	SRM (0.032, 0,0625, 0.125, 0.25, 0.5, 1 mg/ml, addition to the solution) Quercetin (//) BHT (//)	N/N	DPPH solution, ND	//	DPPH radicals scavenging assay/Reduction of DPPH free radicals
		MG (0.5, 1, 2, 4 mM, addition to the cell culture)	SRM (0.5, 1, 2, 4 mM, addition to the solution) Quercetin (//) BHT (//)	//	ABTS solution + trolox, ND	//	ABTS antioxidant assay/High TEAC
		MG (0.0625, 0.125, 0.25, 0.5, 1 mg/ml, addition to the cell culture)	SRM (0.0625, 0.125, 0.25, 0.5, 1 mg/ml, addition to the solution) Quercetin (//) BHT (//)	//	FeCl3 solution, ND	//	FRAP (+)

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Other effects							
Grewal (1932b)	MG pharmacology	MG fumarate (1:2000, 1:4000, 1:7000, 1:10,000, 20,000, 1:40,000, 1:50,000, 1:66,000, 1:100,000, 1:200,000, dilution)	Quinine Hydrochloride (1:2000, 1:4000, 1:7000; 1:10,000, 20,000, 1: 40,000, 1:50,000, 1:66,000, 1:100,000, 1:200,000, dilution)	N/N	Paramecia, ND	ND	ND/Death
		MG fumarate (1:250, 1:330, 1:500, 1:1,000, 1:2,000, dilution)	ND (ND)	//	Staphylococcus Albus and B. coli, ND	//	ND/No growth at the highest dilution
		MG fumarate (1:20,000–1:100,000, dilution)	Ringer solution (ND) Urethane (5%, ND)	//	Rabbit's isolated intestine, ND	//	ND/Decreased amplitude of movements and muscle tone
		MG fumarate (15–20 mgm, i,v.)	Ringer solution (ND)	//	Decerebrated cats' intestine, ND	//	Intestinal movement by balloon method/Decrease
		MG fumarate (ND, dilution)	Ringer solution (ND)	//	Muscle tissue (Guinea pig's isolated uterus, strips of rabbit's bladder), ND	//	ND/Muscle relaxation
		MG fumarate (1:15,000, ND) or (1:10,000, dilution)	Ringer solution (ND)	//	Frog stripped muscle (Gastrocnemii, Sartorius, Hipoglossus), ND	//	–
		MG fumarate (ND, dilution)	//	//	Frog, rabbits, cats, ND	//	Perfused heart trough hepatic vein/Reduction of contraction
		MG fumarate (2.5, 5 mg, i,v.)	Urethane (ND)	//	Anesthetized frog, rabbits, cats, ND	//	ECG, pulmonary artery pressure, blood pressure/ Fall of blood pressure with an increase in cardiac output
		MG fumarate (1.0%, 0.1%, 0.01%, instillation)	Ringer solution (ND)	//	Rabbit's cornea, ND	//	ND/Local anesthetic effect

(Continues)

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Other effects							
		MG (1: 10,000, ND)	ND (ND)	//	Frog's sciatic nerve, ND	ND	Excitability and conduction (0)
		MG (5 mgm, Inj)	Urethane (ND)	//	Rabbits, mice and frogs, ND	ND	Faradic stimulation of the central end of right vagus/ Reduction of the threshold, vasodilatation
		MG (2.5, 5 mg, Inj)	ND (ND)	//	Injection into the jugular vein, ND	//	Stimulation of the chorda tympani for 10 s/ Autonomic effect
		MG (15 mg/kg, ND)	//	//	Rabbits, ND	//	Observation/Weight loss, coat deterioration
Hazim et al. (2011)	Effects on exploratory behavior, short-term memory and motor coordination	MG (20, 40, 80 mg/kg, p.o.) MS Alk-E (20, 40, 80 mg/kg, p.o.)	Amphetamine (10 mg/kg, i.p.) Scopolamine (1 mg/kg, i.p.)	N/Y	Swiss Albino mice, 9 (9)	Spontaneous locomotor activity	Y-maze test/Increased spontaneous locomotor activity and novelty-induced rearing behavior
		MG (20, 40, 80 mg/kg, p.o.) MS Alk-E (20, 40,80 mg/kg, p.o.)	Diazepam (5 mg/kg, i.p.)	//	Swiss Albino mice, 8 (9)	Motor coordination	Rota-Rod test (0)
Hazim et al. (2014)	Effect on anxiety-related behaviors	MG (10, 20, 40 mg/kg, p.o.)	Diazepam (10 mg/kg, p.o.)	N/Y	Sprague–Dawley rats, 5 (8)	Anxiety	OF test/Increase in CZE and % CZT; EPM test/Increase in %OAE and %OAT
Idayu et al. (2011)	Antidepressant effect and effect towards the HPA neuroendocrine system	MG (5, 10, 30 mg/kg, i.p.)	Fluoxetine (20 mg/kg, i.p.) Amitriptyline (10 mg/kg, i.p.)	N/Y	ICR mice, 6 (8)	Depression; FST or TST induced stress	FST, TST/Reduction of immobility time (comparable to fluoxetine and amitriptyline); Corticosterone serum level/Reduction
		MG (5, 10, 30 mg/kg, i.p.)	Fluoxetine (20 mg/kg, i.p.) Amitriptyline (10 mg/kg, i.p.) Amphetamine (1 mg/kg, i.p.)	//	ICR mice, 7(8)	Anxiety	OF test (0)
Juanda et al. (2019)	Potential antibacterial activity	MS ME (3%, 6%, 9%, 12%, 15%, 18%, 21%, 24%, 27%, 30% of 62.27 g, addition to the suspension)	ND (ND)	Y/N	Aeromonas hydrophilla, ND	ND	Agar diffusion method using the NA medium/Growth inhibition and death

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Other effects							
Khor et al. (2011)[a]	See WD section						
Kumarnsit et al. (2006)	Effect on food, water intake and bodyweight	MSE (15, 30, 45, 50 mg/kg, i.p.)	Imipramine (40 mg/kg, i.p.)	Y/N	Wistar rats, 6 (10)	ND	Food, water intake and bodyweight measurement/Decrease
		MSE (40 mg/kg, i.p.)	ND (ND)	//	Wistar rats, 2 (10)	//	–
Kumarnsit et al. (2007a)	Effect on EW	MS AE (100, 300, 500 mg/kg, intragastrically)	ND (ND)	N/Y	Swiss albino mice, 4 (10)	Depression	TST/Reduced immobility duration
Kumarnsit et al. (2007b)	Stimulant effect on the dorsal raphe nucleus and antidepressant-like activity	MSE (60, 90 mg/kg, i.p)	ND (ND)	Y/N	Wistar rats, 3 (7-10)	Depression	FST/Reduced immobility time
		MSE (40 mg/kg, i.p.)	//	//	Wistar rats, 3 (7)	ND	Fos-like immunoreactivity/Induction in the dorsal raphe nucleus of rats chronically injected
Macko et al. (1972)[a]	MG pharmacology	MG (ND, p.o.)	Codeine (ND, p.o.)	ND	Dogs, ND	Cough	Electromagnetically evocated cough reflex/Inhibition
		MG (ND, p.o.)	ND (ND)	//	Rat, ND	Inflammation	Paw-pressure test/Inhibition
Moklas et al. (2013)	Effect on cognitive and behavioral performances	MS ME (10 mg/kg, 30 mg/kg, 100 mg/kg, p.o.)	MS AE (10 mg/kg, 30 mg/kg, 100 mg/kg, p.o.)	Y/N	Sprague Dawley rats, 7 (ND)	Anxiety; locomotor activity; cognitive performance	EPM test/Increase in %OAE and %OAT; number of crossing/Reduction; novel-object discrimination test (–)
		MS ME (10 mg/kg, 30 mg/kg, 100 mg/kg, p.o.) MS AE (10 mg/kg, 30 mg/kg, 100 mg/kg, p.o.)	Scopolamine (ND, i.p.)	//	ICR mice, 8 (ND)	Rota-rod performance	Time of falling from the revolving rotarod/Sedative effects
Mossadeq et al. (2009)[a]	Anti-inflammatory activity	MS ME (50, 100, 200 mg/kg, i.p.)	ASA (100 mg/kg, i.p.)	Y/N	Sprague-Dawley rats, 5 (8)	Acute and chronic inflammation	Carrageenin-induced paw edema and cotton pellet-induced granuloma/Inhibition
Parthasarathy et al. (2009)	Antioxidant and antibacterial activity	MS AE or ME or Alk-E (0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.05, 0.01 mg/ml, addition to the solution)	BHT (ND, addition to the solution)	N/Y	DPPH solution, 2.5 ml	Antioxidant activity	DPPH radicals scavenging assay/Inhibition

(Continues)

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Other effects							
		MS AE (25 ml at 100 mg/ml concentration, disk impregnation)	Cloram Phenicol (30 mg/ml, disk impregnation)	//	Salmonella Typhi, Bacillus subtilis, Escherichia Coli, Pseudomonas Aeruginosa strains,10_6 CFU bacteria	Antimicrobial activity	Disk diffusion assay (0)
		MS ME or Alk-E (25 ml at 100 mg/ml concentration, disk impregnation)	Cloram Phenicol (30 mg/ml, disk impregnation)	//	//	//	Disk diffusion assay/Great inhibition zone (Salmonella Typhi, Bacillus subtilis)
Salleh et al. (2011)	Potential antipyretic properties	MS crude ME (50 mg/kg, 100 mg/kg, 200 mg/kg, i.p.)	Ketoprofen (1 mg/kg, i.p.)	N/Y	BALB/c mice, 5 (6)	Brewer's yeast-induced pyrexia	Rectal temperature recording/Reduction
Senik et al. (2012)	Effect on cognitive function	MS ME (100, 500, 1000 mg/kg, p.o.)	MOR (430 mg/kg, p.o.) Piracetam (500 mg/kg, p.o.)	N/Y	(Albino) Sprague-Dawley rats, 6 (10)	Learning; long term memory	One-way PA test and two-way active avoidance test/Learning acquisition (+)
Tsuchiya et al. (2002)	Effect on gastric acid secretion	MG (30 mg, i.c.v.) MG (3, 10, 30 mg, i.c.v.)	ND (ND)	N/Y	Wistar rats, 2 (7–9)	ND	Basal gastric acid secretion (0)
		MG (30 mg, i.c.v.) MG (3, 10, 30 mg, i.c.v.)	MOR (1, 3, 10 mg, i.c.v.)	//	Wistar rats, 6 (3–7)	//	2-deoxy-D-glucose-stimulated gastric acid secretion/Inhibition
Vázquez López et al. (2017)	Action on stress	MG + paynantheine solution (1 mg/kg + 0.05 mg/kg, i.p.)	Ethanol (3 v/v%, i.p.)	N/N	WT mice, 2 (9–15) mu-opioid receptor KO mice, 2 (9–15)	ND	Vocalization threshold in response to electrical stimulation of the tail root/Basal response current (mA) and AI (0)
		MG + paynantheine solution (1 mg/kg + 0.05 mg/kg, i.p.)	Ethanol (3 v/v%, i.p.)	//	(Stressed and not stressed) WT mice, 2 (9-15) mu-opioid receptor KO mice, 2 (9–15)	Restraint–stress-induced analgesia	Vocalization threshold in response to electrical stimulation of the tail root/Reduction of AI

TABLE 1 (Continued)

Author	Research Question	Studied Compound (Dose, Route)	Positive Control (Dose, Route)	SAL/VEH	Animal, Tissue Type, Groups (Sample Size)	Clinical Model	Test/Measures
Other effects							
Vijeepallam et al. (2016)	Antipsychotic-like effect	MS ME (50, 75, 100, 125, 250, 500 mg/kg, p.o.)	ND (ND)	Y/Y	Swiss albino mice, 8 (8)	(ApoMOR-induced) climbing behavior	Climbing behavior index/ Attenuation
		MS ME (75, 100 mg/kg, p.o.)	//	//	Swiss albino mice, 4 (8)	(Haloperidol-induced) catalepsy	Mouse bar test/Potentiation of catalepsy
		MS ME (50, 75, 100, 125, 250, 500 mg/kg, p.o.)	Clozapine (1 mg/kg, p.o.)	//	Swiss albino mice, 9 (8)	(Ketamine-induced) social withdrawal	Social behavior observation/ Social interaction (+) and withdrawal reduction
Yuniarti et al. (2020)	Antioxidant activity	Kratom leaf ethanol extract (20, 40, 60, 80 and 100 μg/ml, ND)	Vitamin C	N/N	DPPH solution, ND	Antioxidant activity test	DPPH radicals scavenging assay, + or - Vitamin C/ High reduction of DPPH free radicals

Note: %OAE: open arm entries; %OAT: time spent on open arms; %CZT: time spent in central zone; //: same data as above; -: impairment; 0: no effect.

Abbreviations: 2-AA, 2-aminoanthracene; 2-NF, 2-Nitrofluorene; 5-FU, 5-Fluoruracil; 5-HETE, 5-hydroxy-6,8,11,14-eicosatetraenoic acid; 7HMG, 7-hydroxymitragynine; ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); AE, aqueous extract; AI, analgesic index; Alk-E, alkaloid extract; ASA, acetylsalicylic acid; BA, betulinic acid; BHT, butylated hydroxytoluene; CAMP, cyclic adenosine monophosphate; CCK, cholecystokinin; CLAMS, comprehensive lab animal monitoring system; CFU, colony forming units; CP, Conditioned place preference; CREB, cAMP response element binding; CZE, number of entries in central zone; DPPH, 1,1-diphenyl-2-picryl hydrazylfree; ED, ethanol dependent; EPM, elevated plus-maze; ET, ethanol treatment; EW, ethanol withdrawal; FR, fixed-ratio; FRAP, ferric reducing antioxidant power assay; FST, forced swim test; HPA, hypothalamic-pituitary-adrenal; HPT, hot plate test; i.c.v., intracerebroventricular; i.p., intraperitoneal; i.v., intravenous; Inj, injection; KO, knock-out; LKT, lyophilized kratom tea; LFP, local field potential; ME, methanol extract; MG, mitragynine; MGM-15, (E)- methyl 2-((2S,3S,7aS,12aR,12bS)-3-ethyl-7a-hydroxy-8-methoxy-1,2,3,4,6,7,7a,12,12a,12b-decahydroindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate; MGM-16, (E)-methyl 2-((2S,3S,7aS,12aR,12bS)-3-ethyl-9-fluoro-7a-hydroxy-8-methoxy-1,2,3,4,6,7,7a,12,12a,12b-decahydroindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate; 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; MOR, morphine; MS, *Mitragyna speciosa*; MSE: *Mitragyna speciosa* extract; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NAL, naloxone; NaN3, sodium azide; OF, open field; p.o., per oral; PA, passive avoidance; RA, retinoid acid; s.c., subcutaneous; SAL, saline solution; SRM, silane reduced analogue; TEAC, high trolox equivalent antioxidant capacity; TFT, tail flick test; TPT, tail pinch test; TST, tail suspension test; VEH, vehicle; WD, withdrawal and dependence; WIR, water immersion restraint; WT, wild type.

[a]record with more than 1 evidence, the content is reported in the specific section.

learning impairment (Singh et al., 2019c), severe-to-moderate dependence (Singh et al., 2014), with severe dependence negatively affecting physical well-being (Leong Bin Abdullah et al., 2019a). Concerns during kratom cessation were physical (e.g., muscle spasms, pain, watery eyes and nose, fever, diminished appetite, gastrointestinal effects-diarrhea, constipation-, and severe fatigue) (Singh et al. 2014, 2018d, 2019a), and psychological withdrawal symptoms, for example, sleep problems, restlessness/nervousness, anger (Singh et al., 2014, 2018d), and mild levels of anxiety and depression (Singh et al., 2018c). Some of these adverse effects were described as linked to a greater kratom tea/juice daily consumption (Singh et al., 2018a, 2018c, 2018d, 2019a) or a major daily use frequency (Leong Bin Abdullah et al., 2020a).

Further, evidence of severe psychosis (Leong Bin Abdullah et al., 2019b) and electrocardiogram (ECG) alterations (Leong Bin Abdullah et al., 2020b) was found to be not related to kratom use. Additionally, kratom was not found to have a negative impact on life quality (Leong Bin Abdullah et al., 2019a), nor causing any alterations of hepatic (Leong Bin Abdullah et al., 2020a) or other biochemical parameters (Singh et al., 2018a), hormones levels (testosterone, FSH and LH; Singh et al., 2018b), social functioning in a traditional setting (Singh et al., 2015), motor function, and cognitive profile concerning attention, working memory, and executive functions (Singh et al., 2019c).

Among the experimental studies, evidence of potential therapeutic applications was shown in two studies. In fact, in the interventional study performed by Grewal (1932a), participants ($N = 5$) were orally administered mitragynine acetate (0.05 g–50 mg) or MS powdered leaves (0.65, 1.3 g), and kratom was found to reduce heat sensitivity and electrical resistance of the skin, to improve muscular work, and to cause dilatation of the skin blood vessels (Grewal, 1932a). Furthermore, some safety issues were reported by Grewal (1932a), such as giddiness, slight sight's alterations and nystagmus, muscle tenseness, pupils contraction, hand/tongue's tremor, stomach irritation and nausea, sleepiness sensation, and distorted motor coordination at higher doses (Grewal, 1932a). However, the adverse effects reported by Grewal (1932a) came from a small sample ($N = 5$) and cannot be generalized.

Vicknasingam et al. (2020) did not report any safety issues in a recent Randomized Controlled Trial (RCT) with participants being administered three kratom decoction drinks (mitragynine dose is not described). They found that kratom increased tolerance to cold-evoked pain one hour after administration, without reporting discomforts nor withdrawal symptoms for at least 20 h (Vicknasingam et al., 2020). Finally, Trakulsrichai et al (2015) performed a prospective study on 10 participants, which were administered one dose (range 6.25–11.5 mg) per day for one week and a final dose on the eighth day (range 6.25–23 mg). This study did not show any therapeutic application but, in the absence of any serious adverse effect, reported some minor safety issues after kratom administration, such as a temporary blood pressure/heart rate increase and tongue numbness. Other details are provided in Table 2.

4 | DISCUSSION

To our knowledge, this is the first systematic review that provides an overview of (pre)clinical evidence of mitragynine/kratom therapeutic use and safety issues in humans. Among the records included in this analysis ($N = 75$), 24% provided data in humans, while 76% supported its potential therapeutic use in the treatment of either acute and chronic pain (41%), substance use disorders (25%), such as morphine withdrawal and dependence, ethanol withdrawal, seeking behavior and intake; and other medical conditions based on several kratom effects (46%). Two out of the 18 clinical studies reported evidence of potential therapeutic application in pain. In contrast, some issues chronic kratom use related, such as learning impairment, alterations of cholesterol level, dependence, and withdrawal symptoms, were reported in 50% of them.

Many plant-based medicines, including kratom, have historically been used in tropical regions to treat common health problems (Brown et al., 2017). However, over the years, its use has been become diffuse also in Western countries for both recreational and self-medicating purposes. Among the latter, the most commonly reported by users is pain relief (Grundmann, 2017; Schimmel et al., 2020; Singh et al., 2020).

The antinociceptive effects of kratom preparations, such as mitragynine (Carpenter et al., 2016; Criddle, 2015; Fakurazi et al., 2013; Foss et al., 2020; Hiranita et al., 2019; Idid et al., 1998; Macko et al., 1972; Matsumoto et al., 1996a, 1996b; Shamima et al., 2012; Thongpradichote et al., 1998), LKT (Wilson et al., 2020), MG Pseudoindoxyl (Takayama et al., 2002), MGM-9 (Matsumoto et al., 2008), MGM-15 and MGM-16 (Matsumoto et al., 2014), and 7HMG (Matsumoto et al., 2004, 2005, 2006) recently suggested to be the key mediator of mitragynine's analgesic effects (Kruegel et al., 2019), may be considered as preclinical evidence of kratom's potential therapeutic use in pain treatment and would explain why many users claim this benefit. Further, this therapeutic application is supported by two clinical studies that found kratom to reduce pain sensitivity (Grewal, 1932a; Vicknasingam et al., 2020). According to the evidence reviewed in this paper, kratom was reported to exert antinociceptive effects through a multimodal regulation. This is suggested to involve spinal and supraspinal delta-, mu- (Matsumoto et al., 2014; Shamima et al., 2012; Thongpradichote et al., 1998), and potentially kappa-opioid receptors (Wilson et al., 2020) together with α-adrenergic receptors (Foss et al., 2020). Other suggested mechanisms underlying these analgesic properties would include descending noradrenergic and serotoninergic systems (Matsumoto et al., 1996a), Fos expression in the raphe nucleus (Kumarnsit et al., 2007b), neuronal Ca2+ channels blockage (Matsumoto et al., 2005; Takayama et al., 2002), and inhibition of some hyperalgesia mediators involved in anti-inflammatory processes (Mossadeq et al., 2009). In a double connection, it is also suggested that the inhibition of active pain substances release (Aziddin et al., 2005) and a decreased COX-2 mRNA/prostaglandin E_2 production (Utar et al., 2011) would mediate kratom's anti-inflammatory effects, which we found in some studies (Aziddin et al., 2005; Chittrakarn et al., 2018; Macko et al., 1972; Mossadeq et al., 2009). We also found kratom to show some actions suggested to

TABLE 2 Clinical studies

Author	Place	Participants (N, Gender)	K-Use (Time)	Control Group (N, Gender)	Design	Research Question	Studied Compound (Dose, Route)	Administration Time (n)	(Majority of Participants) kratom Daily Consumed (glasses)/ times Daily	Average MG Content X day	Test/ Measures	Safety issues (YES, NO)
Interventional Studies												
Grewal (1932a)	ND	Volunteers (5, male)	ND	ND	Interventional study	Effects on muscular and mental fatigue	MG acetate (0.05 g, p.o.)	1 ($N = 3$); 2 ($N = 2$)	(ND)/ND	ND	Produced symptoms (–)	YES
							MG acetate (50 mg, p.o.)	1 ($N = 3$); 2 ($N = 2$)	(ND)/ND	ND	Choice reaction time (+); heat tolerance (+); weight lift test (+); steadiness (+); dotting test (+/–); electrical skin resistance (+/–); vision test (0)	YES
							MS powdered leaves (0.65, 1.3 g p.o.)	1 ($N = 3$); 2 ($N = 2$)	(ND)/ND	ND	Produced symptoms (= MG)	YES
							MS powdered leaves (0.65, 1.3 g p.o.)	1 ($N = 3$); 2 ($N = 2$)	(ND)/ND	ND	Choice reaction time (–); heat tolerance (change: -); weight lift test (+); dotting test (0); electrical skin resistance (–)	YES/NO
Trakulsrichai et al. (2015)	Thailand	Chronic regular kratom users (10, male)	≥6 months	ND	Prospective study	PK of MG, blood pressure, and pulse rate change after taking kratom	MG (6.25–11.5 mg, p.o. for 7 days + final dose range 6.25–23 mg, p.o.)	Daily (7 days) + 8th day	(ND)/1–9	ND	Blood exams and urine samples (0); observations (-; tongue numbness); safety and vital signs (–)	YES
Vicknasingam et al. (2020)	Malaysia	Regular kratom users (26, male)	≥12 months	ND	Randomized placebo-controlled, double-blind study	Evaluation of changes in pain tolerance, physiologic responses, and in potential withdrawal signs or symptoms	Kratom decoction drink (approximating MG concentration levels found in field decoctions)	3 during the day	(ND)/multiple	ND	CPT (+); blood samples and vital signs (0); COWS (0); subjective symptoms (0)	NO

TABLE 2 (Continued)

Author	Place	Participants (N, Gender)	K-Use (Time)	Control Group (N, Gender)	Design	Research Question	Studied Compound (Dose, Route)	Administration Time (n)	(Majority of Participants) kratom Daily Consumed (glasses)/ times Daily	Average MG Content X day	Test/ Measures	Safety issues (YES, NO)
Observational studies												
Leong Bin Abdullah et al. (2019a)	Malaysia	Regular kratom users (150, male)	≥1 year	ND	Cross-sectional survey	Quality of life of kratom users and its associated factors	ND	ND	>3 glasses/≥4 times daily	ND	WHOQOL-BREF (0; – in severe dependence); KDS (+)	YES
Leong Bin Abdullah et al. (2019b)	Malaysia	Regular kratom users (150, male)	≥1 year	ND	Cross-sectional clinical survey	Prevalence/severity of psychosis/psychotic symptoms in users and the evaluation of associations between K-use and the occurrence of psychotic symptoms	ND	ND	≥4 glasses/>3	ND	BPRS, MINI, DSMV (–; not related to K-use)	NO
Leong Bin Abdullah et al. (2020a)	Malaysia	Regular kratom users (100, male)	≥1 year	Healthy subjects, no K-use (100, male)	Analytical cross-sectional study	Fasting lipid profile of users and its associations with K-use	ND	ND	≥4 glasses/>3	ND	Serum TG and HDL (0); serum TC and LDL (–??); liver parameters (0)	YES
Leong Bin Abdullah et al. (2020b)	Malaysia	Regular kratom users (100, male)	≥1 year	Healthy subjects, no K-use (100, male)	Analytical cross-sectional study	Prevalence of ECG abnormalities and QTc intervals in regular kratom users	ND	ND	≥4 glasses/ND	434.28 mg	ECG sinus tachycardia and borderline QTc intervals (no link with K-use)	NO
Saref et al. (2019a).	Malaysia	Illicit drug users with current K-use (260, male)	≥7 days	ND	Cross-sectional study	Self-report relationship between kratom initiation, illicit drugs use, and HIV risk behaviors	ND	ND	≥2 glasses/≤2	ND	Face-to-face interview drug use (+)	NO
Saref et al. (2019b)	Malaysia	Illicit opioid users with current K-use (163, male)	≥7 days	ND	Cross-sectional study	Self-reported prevalence and severity of opioid-related adverse effects after kratom initiation	ND	ND	≥3 glasses/ND	214.29 mg	Face-to-face interview drug use (+)	NO
Singh et al. (2014)	Malaysia	Regular kratom users (293, male)	>1–3 years	ND	Cross-sectional study	Kratom dependence, withdrawal, and craving	ND	ND	≥3.5 glasses/≥3	276.5 mg	LDQ/severe (>50%)-moderate dependence (45%); MWC (–); MCQ short form/high craving (23%), low craving (77%)	YES
Singh et al. (2015)	Malaysia	Regular kratom users (293, male)	≥6 months	ND	Cross-sectional survey	Kratom effects on social functioning	ND	ND	ND	ND	ASI (0)	NO

TABLE 2 (Continued)

Author	Place	Participants (N, Gender)	K-Use (Time)	Control Group (N, Gender)	Design	Research Question	Studied Compound (Dose, Route)	Administration Time (n)	(Majority of Participants) kratom Daily Consumed (glasses)/ times Daily	Average MG Content X day	Test/ Measures	Safety issues (YES, NO)
Observational studies												
Singh et al. (2018a)	Malaysia	Regular kratom users (58, male)	≥2 years	Healthy subjects, no K-use (19, male)	Cross-sectional study	Kratom effects on hematological and clinical-chemistry	ND	ND	≥3.5/≥2	76.3–114.8 mg	Full-blood test/ Hematological (0) and biochemical parameters (0)	YES
Singh et al. (2018b)	Malaysia	Regular kratom users (19, male)	≥2 years	ND	Cross-sectional study	Kratom effects on testosterone levels after long-term K-use	ND	ND	3.5/ND	76.23–94.15 mg	Full-blood test/ Hematological and biochemical parameters (0); full-blood test/ testosterone, FSH, LH levels (0)	NO
Singh et al. (2018c)	Malaysia	Regular kratom users (150, male)	≥1 year	ND	Retrospective study	Severity of kratom withdrawal symptoms (anxiety and depression)	ND	ND	≥4/≥2	ND	BDI (–); BAI (–)	YES
Singh et al. (2018d)	Malaysia	Regular kratom users (170, male)	>2 years	ND	Cross-sectional study	Severity of kratom withdrawal symptoms (pain, sleep problems)	ND	ND	≥3.5/≥2	76–115 mg	BPI (–); PSQI (–)	YES
Singh et al. (2019a)	Malaysia	Regular kratom users (125, male)	ND	ND	Retrospective study	Constipation prevalence from K-use and fatigue severity during kratom cessation	ND	ND	≥3/ND	ND	CAS (–); FSS (–)	YES
Singh et al. (2019b)	Malaysia	Regular kratom users (62 male, 1, female)	>2 years	ND	Cross-sectional study	K-use dose-dependent effects	ND	ND	≥3 glasses/1-3	ND	B-BAES (0)	YES
Singh et al. (2019c)	Malaysia	Regular kratom users (70, male)	≥2 years	No kratom users (25, male)	Cross-sectional study	Kratom effects on cognitive functions	ND	ND	≤3 glasses/>2	72.5–74.9 mg	CANTAB: PAL (–); MOT (0); DMS (0); SWM (0); RTI (0); AST (0)	YES

Note: (n): number; (*N* =): subjects; -: impairment; +: improvement; 0: no effect.

Abbreviations: ASI, addiction severity index; AST, attention switching task; BAI, Beck anxiety inventory; B-BAES, brief-biphasic alcohol effects scale; BDI, Beck depression inventory; BPI, brief pain inventory; BPRS, brief psychiatric rating scale; CANTAB, Cambridge neuropsychological test automated battery; CAS, constipation assessment scale; COWS, clinical opioid withdrawal scale; CPT, cold pressor task; DMS, delayed matching to sample; DSMV, diagnostic and statistical manual of mental disorders V edition; ECG, electrocardiogram; FSH, follicle stimulating hormone; FSS, fatigue severity scale; K-use, kratom use *(time is based on study's inclusion criteria)*; KDS, kratom dependence scale; LDQ, leeds dependence questionnaire; LH, luteinizing hormone; MCQ, marijuana craving questionnaire; MG, mitragynine; MINI: mini international neuropsychiatric interview; MOT, motor screening task; MS, *Mitragyna speciosa*; MWC, marijuana withdrawal checklist; PAL, paired associates learning; PK, pharmacokinetics; PSQI: Pittsburgh sleep quality index; RTI, reaction time; SWM, spatial working memory; TC, total cholesterol; TG, triglycerides; WHOQOL-BREF, World Health Organization quality of life- BREF.

be possibly involved in pain reduction with herbal remedies (Forouzanfar and Hosseinzadeh, 2018), such as muscle relaxant effects by acting on the neuromuscular junction (Chittrakarn et al., 2010), and antioxidant properties potentially related to phenolic content (Ghazali et al., 2011; Goh et al., 2014; Grewal, 1932b; Parthasarathy et al., 2009; Yuniarti et al., 2020).

In preclinical studies, kratom was found to reduce ethanol (Cheaha et al., 2015; Gutridge et al., 2020; Kumarnsit et al., 2007a; Vijeepallam et al., 2019) and morphine (Cheaha et al., 2017; Fakurazi et al., 2013; Harun et al., 2020; Hassan et al., 2020; Hemby et al., 2019; Jamil et al., 2013; Khor et al., 2011; Meepong and Sooksawate, 2019; Wilson et al., 2020; Yue et al., 2018) withdrawal and dependence as well. First, it has been suggested that kratom may reduce opioid dependence by acting on mu- and delta-opioid receptors (Harun et al., 2020; Hemby et al., 2019), inducing cAMP pathway down-regulation (with CREB would be the basis of tolerance and dependence), and reducing mRNA mu-opioid receptor expression (Fakurazi et al., 2013; Jamil et al., 2013), and/or avoiding the acquisition/expression of morphine-induced CPP (Meepong and Sooksawate, 2019). The mitigation of opioid withdrawal has been suggested to be dependent on mu-, delta- (Hazim et al., 2011), and kappa-opioid receptors, but also both kratom anxiolytic (Khor et al., 2011; Meepong and Sooksawate, 2019) and antidepressant activity through the serotonergic system (Cheaha et al., 2017) may be involved. The latter mechanism is presumed to be also involved in ethanol withdrawal (Cheaha et al., 2015; Kumarnsit et al., 2007a); the alcohol intake reduction was described to be mainly mediated by delta-opioid receptors (Gutridge et al., 2020).

These findings provide some initial evidence for the therapeutic use of kratom in the treatment of both opioid and alcohol withdrawal and dependence, and support the empirical use of kratom in self-treating of drugs/opioid detoxification and withdrawal as mainly reported by users (Bowe and Kerr, 2020; Boyer et al., 2008, 2007; Grundmann et al., 2020; Schimmel et al., 2020; Singh et al., 2020). Further, among studies conducted in users in our analysis, 12% showed an association between kratom initiation and reduction in the prevalence of adverse effects related to opiates (e.g., respiratory depression, constipation, physical pain) (Saref et al., 2019b), and either in regular drugs use (Saref et al., 2019a). According to Saref et al. (2019a), this evidence suggests that kratom may also be a useful agent, less risky than opioids, for harm-reduction purposes (Saref et al., 2019a). This data may be supported by the findings of a recent study that showed LKT to induce fewer side effects (e.g., physical dependence/respiratory depression) compared to MOR without affecting motor activity (Wilson et al., 2020). Similarly, some authors reported that mitragynine is a compound with a minor addictive potential (Meepong and Sooksawate, 2019; Thériault et al., 2020; Yue et al., 2018), when compared to MOR (Cheaha et al., 2017; Harun et al., 2015), neither it caused physiological dependence (Harun et al., 2020). Moreover, despite kratom and 7HMG were reported to have rewarding effects (Gutridge et al., 2020), with 7HMG having a higher abuse potential (Hassan et al., 2019; Sabetghadam et al., 2013; Yusoff et al., 2016), a recent study found that both mitragynine and 7HMG did not show rewarding actions in the intracranial self-stimulation (Behnood-Rod et al., 2020).

Furthermore, kratom has also been presumed to act on the serotoninergic/adrenergic system and dorsal raphe nucleus (Kumarnsit et al., 2007a, 2007b), and to lessen both corticotrophin-releasing factor (CRF) and prodynorphin mRNA expression by acting on the hypothalamic-pituitary-adrenal axis (HPA) in the Central Nervous System (CNS) (Idayu et al., 2011; Khor et al., 2011). These mechanisms are reported to mediate stress mitigating (Hazim et al., 2011; Khor et al., 2011; Vázquez López et al., 2017), anxiolytic-like (Hazim et al., 2014; Khor et al., 2011; Moklas et al., 2013), and antidepressant-like effects (Idayu et al., 2011; Kumarnsit et al., 2007a, 2007b). These effects, together with kratom's antipsychotic-like effects through 5-HT2 and D2 receptors inhibition (Vijeepallam et al., 2016), may be considered as preclinical evidence of kratom's potential therapeutic use in psychiatric disorders as well since many users claim kratom's benefits to self-treat depression, anxiety and attention deficit hyperactivity disorder (ADHD) (Bath et al., 2020; Veltri and Grundmann, 2019). That is linear with the idea reported in the literature that some plants such as kratom, having an indole moiety like common antidepressant drugs, might be a potential alternative plant-based remedy for treating depression (Hamid et al., 2017) and psychological disorders (Johnson et al., 2020).

Then, we found kratom to exert therapeutic effects in additional medical domains. These included a peptic ulcer protective action (Chittrakarn et al., 2018) and acid gastric secretion inhibition (Tsuchiya et al., 2002), with a possible indirect anorectic action (Chittrakarn et al., 2008; Grewal, 1932b; Kumarnsit et al., 2006, 2007b), antidiarrheal effect (Chittrakarn et al., 2008), anthelmintic (Abdul Aziz et al., 2012), antibacterial effects (Juanda et al., 2019; Parthasarathy et al., 2009), antipyretic (Salleh et al., 2011), anti-mutagen/anticancer (Ghazali et al., 2011; Goh et al., 2014), antitussive (Macko et al., 1972), and antihypertensive effect (Grewal, 1932b), that appear in line with the traditional application of the plant for treating stomach ailments, diabetes, diarrhea, infections, fever, cough, hypertension (Brown et al., 2017; Eastlack et al., 2020; Hassan et al., 2013; Kruegel and Grundmann, 2018; Ramachandram et al., 2019; Saref et al., 2019a; Singh et al., 2017, 2020; Suhaimi et al., 2016; Vicknasingam et al., 2010). It was also found of potential benefit in treating COVID-19 symptoms (Metastasio et al., 2020).

Finally, the facilitation of learning through the modulation of memory consolidation (Senik et al., 2012) may provide preclinical evidence of kratom on nootropic effects. This data was also confirmed in other preclinical studies where kratom showed cognitive enhancing properties (Hazim et al., 2011; Ilmie et al., 2015). Further, kratom use did not seem to have long-term cognitive effects on users, but it was found to affect only visual episodic memory causing learning impairment in chronic users with at least two years of use (Singh et al., 2019c). This latest data is in strong contrast with preclinical evidence related to kratom's potential to enhance cognition but appears linear with the cognitive impairment described in preclinical studies with both chronic (Apryani et al., 2010; Compton et al., 2014; Hassan et al., 2019; Ismail

et al., 2017; Yusoff et al., 2016) and acute (10, 30, 100 mg/kg, p.o.) (Moklas et al., 2013) administration of the preparation. It is possible to say that findings are inconsistent, and kratom's significant cognitive impact needs to be further investigated.

On the other side, clinical studies related to therapeutic applications are lacking as well. In the analyzed studies, most participants consumed ≥ two-to-three glasses of kratom 1–3 times daily with a mitragynine content ranging between a minimum of 72.5 mg and a maximum of 434.28 mg. However, data about the consumed amount was only reported in few studies (Leong Bin Abdullah et al., 2020b; Saref et al., 2019b; Singh et al., 2014, 2018a, 2018b, 2018d, 2019c).

Further, adverse events such as alterations of cholesterol level, dependence, and withdrawal symptoms were reported and described as mild and dependent on higher doses (Singh et al., 2018a, 2018c, 2018d, 2019a) or more frequent use (Leong Bin Abdullah et al., 2020a, 2020b). This suggests that these adverse events may not occur at lower doses used with less frequency. These findings confirm that those who use kratom in traditional settings regularly could experience kratom cessation related concerns, as previously reported (Saingam et al., 2016; Vicknasingam et al., 2010), but evidence suggests that most of them self-manage their symptoms (Singh et al., 2014, 2015), and experience more tolerable pain when compared to opioids (Singh et al., 2018d). However, a physical well-being impairment has been reported only in severe kratom dependence (Leong Bin Abdullah et al., 2019a). Vicknasingam et al. (2020) did not find withdrawal symptoms in the observation period (20 h), and Trakulsrichai et al. (2015) did not describe serious adverse events in humans.

Case reports in the literature showed other health problems related to chronic kratom use, such as hepatic damage, endocrinologic issues (e.g., hypogonadism and hypothyroidism), neurological disorders, such as posterior reversible leukoencefalopathy syndrome, seizure and coma, pulmonary (e.g., acute respiratory distress syndrome, ARDS), and cardiovascular problems (Alsarraf et al., 2019; Anwar et al., 2016; Schimmel and Dart, 2020). However, these concerns were mainly reported by users in Western countries, who besides the potential risks, would stress the plant's beneficial effects as well.

4.1 | Limitations

Our review has some limitations. First, findings from preclinical studies are not always comparable due to methodological limitations linked to the studied compounds/preparations, ways of administration, and the variability of the extract composition as it may contain other alkaloids like paynantheine, corynantheidine and speciociliatine, speciogynine, mitragynaline, and corynantheidaline (Takayama, 2004). Thus, this limits strong conclusions about the effect of mitragynine on the investigated domains. Second, all clinical studies were performed in chronic kratom users, in Southern East Asia, with three out of them (only one RCT) studying kratom acute effects, while no one tested long term effects of single/repeated administration nor RCTs have been conducted in kratom naive participants. Most of the other clinical studies had a cross-sectional design, which does not allow a definitive causal interpretation of a direct link between kratom consumption and health consequences, providing mainly retrospective information in terms of kratom's exposure. However, this is not generalizable to the population that occasionally uses kratom in traditional settings, nor to those that use it in non-traditional settings in the West, where available kratom products may differ in terms of potency. Moreover, the almost complete absence of female participants should be considered in further studies to understand gender-related variation in metabolism and pharmacology.

5 | CONCLUSIONS

Taken together, our findings help to explain, but not endorse, the empirical medical use reported by kratom users in non-medical settings in both Asian traditional and Western countries, suggesting that kratom could be a useful aid in the treatment of acute/chronic pain, opioid and substance use disorders, and psychiatric disorders. Kratom-related safety issues must be carefully considered. Until now, mitragynine and kratom's benefits and safety profile remain largely anecdotal. More studies should be encouraged with different populations, including kratom-naive users in controlled clinical settings, to identify better mitragynine and kratom's risks and benefits.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper or that could be perceived as prejudicing the impartiality of the research reported.

ETHICS STATEMENT

The authors declare that human ethics approval was not needed for this study.

AUTHORS CONTRIBUTIONS

Conceptualization, investigation, and methodology: Elisabeth Prevete, Eef L. Theunissen, Kim P. C. Kuypers, Johannes G. Ramaekers. *Writing-Original Draft Preparation:* Elisabeth Prevete. *Writing-Review and Editing:* Elisabeth Prevete, Eef L. Theunissen, Kim P. C. Kuypers, Giuseppe Bersani, Johannes G. Ramaekers, Ornella Corazza. *Supervision:* Johannes G. Ramaekers.

AUTHORS NOTE

The authors confirm that this work is original and has not been published elsewhere. It is currently not under consideration for publication elsewhere, or in press at other journals.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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APPENDIX

Abbreviations

5-HT	serotonin
7HMG	7-hydroxymitragynine
α2	adrenenergic
A2A	adenosine
ADD	attention deficit disorder
ADHD	attention deficit hyperactivity disorder
ARDS	acute respiratory distress syndrome
CNS	central nervous system
COX-2	cyclooxygenase-2
CPP	conditioned place preference
CREB	cAMP response element binding
CRF	corticotrophin releasing factor
CSA	controlled substances act
CYP450	cytochrome P450
D2	dopamine
DEA	drug enforcement administration
ECG	electrocardiogram
FDA	food and drug administration
FSH	follicle stimulating hormone
HPA	hypothalamic-pituitary-adrenal axis
i.p.	intraperitoneal administration
i.v.	intravenous
LH	luteinizing hormone
LKT	lyophilized kratom tea
MeSH	medical subject headings
MG	mitragynine
MGM-15	(E)-methyl 2-((2S,3S,7aS,12aR,12bS)-3-ethyl-7a-hydroxy-8-methoxy-1,2,3,4,6,7,7a,12,12a,12b-decahydroindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate
MGM-16	(E)-methyl 2-((2S,3S,7aS,12aR,12bS)-3-ethyl-9-fluoro-7a-hydroxy-8-methoxy-1,2,3,4,6,7,7a,12,12a,12b-decahydroindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate
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]
MOR	morphine
MS	*Mitragyna speciosa*
p.o.	oral administration
RCT	randomized controlled trial
T1/2	half-life
US	United States