Review Article

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Current perspectives on the therapeutic potential of *Mitragyna speciosa* and its derivatives on animal model

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ABSTRACT

The plant *Mitragyna speciosa* Korth. is receiving increased attention as a therapeutic substitution for opioid use disorder (OUD). The active alkaloids constituents of the plant, particularly mitragynine and 7-hydroxymitragynine, have been shown to modulate opioid receptors, acting as agonists at mu-opioid receptors. Given this pharmacology, several studies have examined the abuse and dependence potential of *M. speciosa* and its alkaloids in various animal models of dependence. In addition to action on opioid receptors, the Mitragyna alkaloids also appear to exert diverse activities at other receptors in the central nervous system which may explain the complex pharmacological profile of these alkaloids. Hence, this review aims to provide an overview of the preclinical studies used to study *M. speciosa* dependence potential and describe recent progress made in assessing whether the plant or its active alkaloids can offer alternatives to opioids in the management of OUD. In conclusion, *M. speciosa* Korth. or its compound mitragynine may offer alternatives as a replacement therapy to opioid.

Keywords: Dependence, *Mitragyna speciosa*, mitragynine, morphine, opioid, rats

INTRODUCTION

Opioids, inclusive of heroin, oxycodone, methadone, morphine, hydrocodone, and fentanyl, are powerful painkillers that are highly addictive. These opioids have become the leading cause of drug overdose in the United States (US), indicating a growing crisis of the opioid overdose epidemic.[1] Since millions of people suffering from opioid use disorder (OUD), the US health providers have been prescribing less opioids, which resulted in an unintentional increase in the abuse of other opioid-like substances.[2] Being an opioid-like herbal supplement, *Mitragyna speciosa* Korth. are increasingly sought to manage chronic pain or opioid withdrawal symptoms.

The leaves of the psychoactive plant *M. speciosa* also commonly known as kratom have been used in Southeast Asia regions for centuries.[3,4] Conventionally, it was used to control ailments such as fever, cough, diarrhea, and fatigue, in addition to treat conditions such as diabetes, hypertension, and depression[5,6] when the leaves are consumed by either brewing the leaves into tea or chewed freshly.[4] In addition to its medicinal benefits, *M. speciosa* was also used as an alternative to traditional opiates and as a replacement therapy for opioid dependence.[7,8] The use of the plant has become more widespread in recent years and has increased the market for its products that are available through online platforms as herbal supplements, in the form of powder, pills, capsules, or energy drinks. Given the present opioid abuse epidemic in the US, the use of *M. speciosa* has become increasingly popular when a significant number of users have reported on its use as a tool to stop or reduce the use of prescription or illicit opioids.[9-11] Hence, the increased consumption and demand for *M. speciosa* have accelerated discussion of whether its potential therapeutic value may outweigh its safety risk and abuse potential. The concern is whether the users who try to self-treat opioid withdrawal may possess the risk of developing undesirable *M. speciosa* abuse and dependence. Therefore, the study of its abuse potential is of high priority in relation to public health and has resulted in a number of scientific reviews in recent years. Although no controlled clinical trials have been conducted, the anecdotal reports and surveys conducted may suggest that the adverse

and withdrawal effects are considered to be mild relative to classical opioids.[6,10,12,13]

Dependence and addiction are indeed human phenomena that cannot be simply replicated in a laboratory setting without unavoidable constraints. However, some of the behavioral characteristics of this condition can be suitably modeled in laboratory animals. A wide range of techniques has been developed to model specific aspects of addictive behaviors and has greatly contributed to the understanding of the neurobiological basis of drug taking and of the brain systems involved in the reward properties of psychoactive substances.[14] Thus, various models have been used to clarify the consequences of exposure to *M. speciosa* and its abuse and dependence liabilities. The present review aims to provide recent evidence on the abuse and dependence potential of *M. speciosa* and its active alkaloid constituents and to explore whether these compounds offer an alternative to opioids in the management of OUD.

THE ACTIVE CONSTITUENTS OF *M. SPECIOSA*

The molecular constituents of *M. speciosa* Korth. have been extensively studied, with more than 40 alkaloids have been found in the plant.[15] The most abundant indole alkaloid is mitragynine which makes up approximately two-thirds of the extract, while the rest are paynantheine, speciogynine, speciociliatine, and 7-hydroxymitragynine.[4,16] The presence of these alkaloids is subjected to significant variation among different regional varieties and the maturity of the plant which substantially complicate the interpretation of reported psychoactive effects from the raw plant material. Among all alkaloids, studies have demonstrated that mitragynine and 7-hydroxymitragynine are the major psychoactive constituents for mediating the effects of *M. speciosa* on the central nervous system.[17,18] In particular, 7-hydroxymitragynine has been identified as a potent opioid agonist with efficacy exceeding those of the prototypical opioid agonist morphine.[19]

THE THERAPEUTIC POTENTIAL OF *M. SPECIOSA* AND ITS DERIVATIVES ON ANIMAL MODEL

Tolerance

Tolerance is defined as a decrease in pharmacological response following repeated or prolonged drug exposure, a feature commonly associated with long-term opioid exposure.[20] To date, tolerance to effects of mitragynine in animal models has not been well studied. Several factors such as the exact mechanisms responsible for the development of tolerance, changes in the metabolism of a drug, cellular and molecular changes, or behavioral effects are poorly understood.

However, studies of tolerance on other *M. speciosa* derivatives have been conducted on antinociception. Repeated exposure to 7-hydroxymitragynine (10 mg/kg, s.c., twice daily) for 5 consecutive days developed tolerance to its antinociceptive effects using tail-flick test.[21] In agreement with this finding, ethylene glycol-bridged and C10-fluorinated derivative of mitragynine, and 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] administered twice daily for 5 consecutive days resulted a time-dependent decrease in the antinociceptive effect of mice indicating the development of tolerance to MGM-9.[22] From these findings, the authors concluded that the repeated administration of 7-hydroxymitragynine and MGM-9 developed tolerance similar to that of opioid agonist, morphine. Cross-tolerance also occurred between these two compounds when mice were treated with morphine or 7-hydroxymitragynine for 5 consecutive days which produced tolerance to the antinociceptive effects.[21]

Váradi *et al*. (2016) demonstrated a relatively slow development of tolerance to mitragynine pseudoindoxyl in mice requiring a total of 29 days chronic treatment as compared to morphine tolerance that developed after 5 days. Due to the mixed mu-agonist and delta antagonistic effects of mitragynine pseudoindoxyl, the study suggested that mitragynine pseudoindoxyl might lack tolerance to the antinociceptive effects in mice.[23] Nevertheless, the role of delta-opioid receptors in delaying the mu-opioid receptor-mediated tolerance remains unclear.

In addition, bidirectional interactions between mitragynine and opioid tolerance demonstrated that mice treated with mitragynine alone or in combination of mitragynine (15 and 25 mg/kg, i.p.) and morphine (5 mg/kg, i.p.) for 9 consecutive days showed no significant changes in cyclic adenosine monophosphate (cAMP) and cAMP response element-binding (CREB) expressions in the thalamus and cortex of mice brain. The authors concluded that concomitant administration of mitragynine and morphine effectively prevents the development of tolerance following the downregulation of cAMP levels and the level of CREB expressions.[24] In this regard, it has been proposed that mu-opioid receptors might be desensitized and uncoupled from downstream signaling pathways, instead of downregulating the opioid receptors. Therefore, additional studies focusing on the role of opioid receptors as well as the role of cAMP levels on the mechanism of mitragynine tolerance would be valuable to clarify this finding.

PHYSICAL DEPENDENCE

Development of dependence is an aspect that can be measured objectively in laboratory animals based largely on the chronic exposure to opiate to maintain a physical equilibrium after which abstinence from the drug leads to the onset of withdrawal symptoms.[25] The potential ability of mitragynine to induce physical dependence in laboratory animals has not been thoroughly studied. A recent study by Harun *et al*.[26] was the first to examine the effects related to physiological dependence on mitragynine, using a schedule-controlled behavior in rats. The changes on conditioned behavior in terms of suppression of response rates indicate the emergence of withdrawal which represent drug-induced physical dependence. Unlike morphine, the study found that chronic twice-daily treatment with escalating doses of mitragynine up to 45 mg/kg over 14 days produced little evidence of a disruption on the response rates. The authors hence concluded

the inability of mitragynine to induce spontaneous withdrawal effects in rats.[26] This finding, therefore, correlates with human studies where the symptoms of *M. speciosa* withdrawal were reported as weaker and milder than those reported following opioid discontinuation.[6,10]

Further, mitragynine could also attenuate the disruption of operant-based performances produced by naloxone. Pharmacological challenge with either naloxone (1.0 mg/kg) or rimonabant (1.0 mg/kg) disrupted operant responding in the dependent rats which suggested more intense withdrawal effects than non-precipitated withdrawal. The precipitation of mitragynine withdrawal by naloxone and rimonabant also suggested that both opioid and cannabinoid receptors may be involved in the development of mitragynine dependence.[26] The similar finding of naloxone-precipitated withdrawal symptoms was also demonstrated in repeated jumping behavior of mice treated with mitragynine either acutely or chronically.[27] However, the levels of jumping behavior were significant elevated following administration of relatively high doses of mitragynine (60 mg/kg in acute withdrawal and 30 mg/kg in chronic withdrawal studies). The reduction of morphine withdrawal symptoms by mitragynine was also demonstrated by Meepong and Sooksawate[27] when 10 mg/kg dose of mitragynine was shown to reduce morphine-induced jumping behavior to the same level as chronic treatment of 10 mg/kg of mitragynine alone, while 30 mg/kg mitragynine reduced Straub tail reaction test. Based on these effects, mitragynine is less potent in inducing dependence compared to morphine and it is possible that mitragynine can decrease the intensity of the effect of morphine dependence. The findings that mitragynine can alleviate morphine withdrawal symptoms also further strengthen the therapeutic value of mitragynine as an opioid substitute.

A recent study by Hassan *et al*.[28] also reported similar findings when mitragynine (5–30 mg/kg; i.p.) was able to attenuate acute withdrawal signs in morphine-dependent rats while smaller doses of methadone (0.5–2 mg/kg; i.p.) and buprenorphine (0.4–1.6 mg/kg; i.p.) were necessary to mitigate these effects. However, other behavioral models of dependence such as studies on self-administration are essential to further confirm these findings.

DRUG DISCRIMINATION STUDIES

Drug discrimination is known as a valuable assay in assessing the *in vivo* pharmacology of abused drugs.[29] Harun *et al*.[17] were the first to evaluate the discriminative stimulus effects of mitragynine in rats. The study demonstrated that mitragynine (15 mg/kg, i.p.) can acquire discriminative stimulus properties in a two-lever drug discrimination paradigm in rats. Mitragynine (15 mg/kg, i.p.) was shown to fully substitute for the morphine discriminative stimulus. In addition, there were cross-generalization effects between the two drugs.[17] These findings highlight the similarity of the underlying pharmacological mechanisms that mediate the discriminative stimulus for both drugs and translate well to studies in which humans report the plant having opioid-like effects.[6,11,30] The fact that mitragynine could substitute for morphine discriminative cue also supports human self-reported use as a substitute to opioids.[10] It is worth noting that the effects of mitragynine were partially blocked by naloxone which suggested that opioid receptors seem to be selectively involved in the discriminative stimulus effects induced by mitragynine. Therefore, further studies are required to fully clarify the underlying pharmacological mechanisms of the mitragynine discriminative stimulus.

Another interesting finding from the Harun *et al*.[17] study was that mitragynine stimulus was found to partially generalize to the psychostimulant cocaine, but not for morphine stimulus. In accordance with this finding, Meepong and Sooksawate[27] also revealed that mitragynine dose dependently substituted to the methamphetamine discriminative stimulus. These findings suggest that mitragynine might share similar interoceptive stimulus properties to stimulants despite its different mechanisms of action and chemical structure. Hence, these studies provide evidence for its psychostimulant-like effects of *M. speciosa* Korth. in humans.[31-34]

In addition, a minor alkaloid of *M. speciosa*, 7-hydroxymitragynine was also shown to dose dependently substitute to the morphine stimulus and full generalization to morphine discriminative stimulus was observed at relatively low doses (1 and 3 mg/kg, i.p.) than those required for mitragynine (15 mg/kg, i.p.). Consistently, the opioid antagonist naloxone completely reversed and blocked the substitution effects of 7-hydroxymitragynine to the morphine discriminative stimulus indicating full agonist properties of 7-hydroxymitragynine on mu-opioid receptors.[17,18]

PLACE CONDITIONING PARADIGM

Studies on the addictive potential of *M. speciosa* have been elucidated using a conditioned place preference (CPP) paradigm, where its rewarding properties have been clearly demonstrated.[35,36] Mitragynine has been shown to induce CPP at both 10 and 30 mg/kg doses over eight conditioning sessions.[35] The establishment of mitragynine-induced CPP at 10 mg/kg was blocked by naloxone pre-treatment (0.3 or 1.0 mg/kg), suggesting that it was mediated through opioid receptors. Conversely, naloxone did not block the expression of mitragynine-induced place preference.[37] In addition, a different study reported that baclofen (2.5 and 5.0 mg/kg) blocked the mitragynine-induced place conditioning at 10 mg/kg in rats during acquisition and expression phases in rats.[38] Hence, these findings suggest the involvement of opioidergic and gamma-aminobutyric acid, GABAergic pathways in the rewarding effects of mitragynine.

In contrast, Meepong and Sooksawate[27] reported that only relatively high doses of mitragynine at 30 and 90 mg/kg could establish a CPP. These conflicting results may be due to species difference in the rats (Wistar vs. Sprague Dawley rats). The authors' postulation is further supported by a study in which a significantly higher dose of morphine could induce a place preference effect in Wistar rats compared to Sprague Dawley rats.[39] Meepong and Sooksawate[27] were the first to demonstrate that mitragynine dose dependently attenuated both the acquisition and expression phases of morphine-induced CPP in rats which also suggested the potential therapeutic use of mitragynine as a treatment for opioid addiction.

Sufka *et al*.,[36] using a similar CPP protocol, tested different doses of *M. speciosa* extract, alkaloid fraction and mitragynine, and found that out of the three doses of mitragynine tested (5, 10, and 30 mg/kg), only the highest and lowest doses produced CPP. *M. speciosa* extract and its fraction increased place conditioning but this effect was not statistically significant. The authors hypothesized that the reduced effect of the extract and fraction could be due to lower concentrations of mitragynine or the presence of other psychoactive constituents which interferes with the rewarding effects of *M. speciosa*.[36]

Apart from that, the putative rewarding properties of other *M. speciosa* metabolites and derivatives of *M. speciosa* have also been identified in animal studies. Matsumoto *et al*.[22] demonstrated that 7-hydroxymitragynine (2 mg/kg) induced a significant CPP in mice. In contrast, the ethylene glycol-bridged and C10-fluorinated derivative of mitragynine, MGM-9, did not produce any significant place preference.[22]

SELF-ADMINISTRATION STUDIES

Studies conducted by Hemby *et al*.[18] and Yue *et al*.[40] revealed that mitragynine has a lower abuse potential as compared to 7-hydroxymitragynine with a potential to reduce morphine intake. In the recent report, rats were trained to self-administer morphine (50 or 100 μg/infusion) before it was substituted with saline for the extinction of the responding. Following extinction, rats were allowed to self-administer different doses of mitragynine (25–150 μg/injection) or 7-hydroxymitragynine (2.5–20 μg/injection). Mitragynine could not maintain response rates significantly greater than those obtained with saline, but it was the opposing effect for 7-hydroxymitragynine. This demonstration of high abuse potential for 7-hydroxymitragynine, while establishing lower abuse potential for mitragynine, indicates that mitragynine can be used therapeutically to treat opioid dependence problem.

Rats were then reassessed with morphine self-administration and mitragynine was found to significantly decrease the morphine self-administration. In contrast, the results also showed a significant increase in morphine self-administration following 7-hydroxymitragynine exposure. Both the μ-opioid receptor selective antagonist naloxonazine and the δ-opioid receptor antagonist naltrindole reduced the self-administration of 7-hydroxymitragynine while only naloxonazine decreased morphine self-administration. In another recent study done by Yue *et al*.,[40] mitragynine and heroin self-administration were compared in rats that were trained to self-administer methamphetamine. Both methamphetamine and heroin engendered lever responding to levels greater than those obtained with saline, with the greatest effects at 0.022 and 0.01 mg/kg/injection, respectively. However, mitragynine self-administration was similar to levels observed for saline suggesting low reinforcing effects and minimal abuse potential which was in agreement with the study by Hemby *et al*.[18] Furthermore, when methamphetamine and heroin self-administered rats were given pre-session injections of mitragynine, a decreasing dose-related effect was observed in only the latter study.[40]

BIOCHEMICAL AND ELECTROPHYSIOLOGICAL STUDIES

Pharmacological effects of *M. speciosa* may be mediated through binding to several receptors including opioid, dopamine, serotonin, and adrenergic receptors.[9] Receptor binding study showed that *M. speciosa* possesses a different degree of affinity to all opioid receptors (μ, κ, and δ) and D1 dopamine receptors.[41] At a cellular level, *M. speciosa* extract, mitragynine and paynantheine, showed a minor effect on phosphorylation and signal transduction of μ-opioid receptor in a guanosine 5'-(gamma-thio) triphosphate (35S-GTPγS) binding assay which was not comparable to the specific agonist morphine.[41] Another systematic study was carried out by Kruegel *et al*. on the *in vitro* characterization of opioid receptor pharmacology and signaling of the mitragynine, 7-hydroxymitragynine, and other Mitragyna alkaloids in human embryonic kidney cells expressing human μ-, κ-, and δ-opioid receptors. Both mitragynine and 7-hydroxymitragynine showed partial agonist activity at the μ-opioid receptors, with 7-hydroxymitragynine being the stronger agonist. It was also found that both compounds were competitive antagonists at both κ- and δ-opioid receptors. More interestingly, mitragynine and 7-hydroxymitragynine displayed G-protein-biased signaling at the μ-opioid receptors, a downstream signaling pathway that is different from the induced classical opioid agonists which involves the recruitment of β-arrestin.[42] The recruitment of the β-arrestin pathway is associated with the main opioid side effects, that is, respiratory depression, thus biased agonism of the compounds at opioid receptors may be an advantage. In a study using the semisynthetic compound, mitragynine pseudoindoxyl further supported the signaling bias for G-protein-coupled opioid receptors that do not recruit the β-arrestin.[23]

CAMP overshoot and downregulation of opioid receptors are the basic cellular characteristics of opioid dependence.[43] Short incubation of *in vitro* cells with mitragynine alone inhibits the formation of cAMP.[44,45] When the incubation was prolonged, the cAMP levels increased and μ-opioid receptors were downregulated in a dose-dependent manner. However, mitragynine was less effective compared to morphine which might indicate the lower potency of mitragynine. Compared with morphine, cotreatment, and substitution with mitragynine also reduced the levels of cAMP and downregulation of μ-opioid receptors,[45] suggesting the potential benefit of mitragynine as an opioid replacement therapy.

Among other neural circuits in the brain, the dopaminergic neurons of ventral tegmental area in the mesencephalon that projects to the ventral striatum play a key role in mediating the reinforcing effects of psychoactive drugs.[46] Behavioral plasticity was observed following subchronic mitragynine exposure which suggests sensitization of the dopamine system in the mesencephalon only, as shown by the increased expression of dopamine transporter which is responsible for the synaptic dopamine clearance, and the increased expression of dopamine receptor regulating factor (DRRF) that controls the expression of brain dopamine receptors.[35]

The animal models that associated with the therapeutic potential assessment of *Mitragyna speciosa* Korth and its derivatives are summarised in Table 1.

Table 1: Summary of animal models and the therapeutic potential of *Mitragyna speciosa* and its derivatives

Study (Year)	Studies	Animal models	Test extract	Major findings
Matsumoto *et al*., 2005[22]	Tolerance	Antinociception	7-hydroxymitragynine	Repeated administration of 7-hydroxymitragynine developed tolerance to its antinociceptive effect
				Cross-tolerance of antinociceptive effects between 7-hydroxymitragynine and morphine
Matsumoto *et al*., 2008[23]		Antinociception	MGM-9	Repeated administration of MGM-9 developed tolerance similar to morphine
Váradi *et al*., 2016[24]		Antinociception	Mitragynine pseudoindoxyl	29 days of chronic treatment were required for the development of tolerance, compared to morphine tolerance that developed after 5 days
Fakurazi *et al*., 2013[25]		Antinociception	Mitragynine	The combination of mitragynine and morphine prevents the development of tolerance following the downregulation of cAMP levels and the level of cAMP response element-binding expressions
Harun *et al*., 2020[27]	Physical dependence	Schedule-controlled behavior	Mitragynine	No disruption of operant performances following spontaneous withdrawal
				Disruption of operant performances following naloxone precipitation of chronic withdrawal
				Mitragynine attenuated the naloxone-precipitated morphine withdrawal effects
Meepong and Sooksawate, 2019[28]		Acute and chronic withdrawal assessment	Mitragynine	Repeated jumping behavior was significant at 60 mg/kg dose following naloxone precipitation of acute withdrawal
				Repeated jumping behavior was significant at 30 mg/kg dose following naloxone precipitation of chronic withdrawal
Harun *et al*., 2015[18]	Drug discrimination	Drug discrimination	Mitragynine	Cross-substitution of mitragynine and morphine discriminative cues
				Partial substitution of cocaine to mitragynine discriminative cue
				Partial blockade of the discriminative stimulus effects by naloxone
Meepong and Sooksawate, 2019[28]		Drug discrimination	Mitragynine	Full substitution of mitragynine to methamphetamine discriminative cue
Matsumoto *et al*.[23]	Place conditioning	Conditioned place preference	7-hydroxymitragynine and MGM-9	7-hydroxymitragynine induced conditioned place preference effects in mice
				MGM-9 did not induce significant conditioned place preference effects
Sufka *et al*.[37]		Conditioned place preference	*Mitragyna speciosa* extract, alkaloid fraction, and mitragynine	*Mitragyna speciosa* extract and its fraction increased preference score (conditioned place preference effect) but to a lesser degree than mitragynine
Meepong and Sooksawate, 2019[28]		Conditioned place preference	Mitragynine	Mitragynine dose dependently attenuated acquisition and expression of morphine conditioned place preference
Yusoff *et al*., 2016[36]		Conditioned place preference	Mitragynine	Mitragynine-induced a significant conditioned place preference at doses of 10 and 30 mg/kg
Yusoff *et al*., 2017[38]		Conditioned place preference	Mitragynine	Opioid receptors mediated the acquisition, but not the expression of mitragynine-induced conditioned place preference
Yusoff *et al*., 2018[39]		Conditioned place preference	Mitragynine	Baclofen blocked the acquisition and expression of mitragynine-induced conditioned place preference
Hemby *et al*., 2019[19]	Self-administration	Intravenous self-administration	Mitragynine and 7-hydroxymitragynine	7-hydroxymitragynine, but not mitragynine dose dependently substituted for morphine self-administration
				The reinforcing effects of 7-hydroxymitragynine were mediated in part by μ- and δ- opiate receptors
Yue *et al*., 2018[41]		Intravenous self-administration	Mitragynine	Unlike heroin, mitragynine did not maintain methamphetamine self-administration
				Mitragynine reduced rates of responding that were maintained by heroin

CONCLUSION

The preclinical studies supported the reasons for the use of *M. speciosa* Korth. as a self-treatment of acute and chronic pain as well as the management of opioid withdrawal symptoms. However, the effects of mitragynine in the various rodent models that measure abuse and dependence liabilities have not been systematically evaluated. Several important issues still remain. The intravenous self-administration of mitragynine was demonstrated only in rats with a previous history of opioid self-administration. Hence, this suggests that mitragynine and *M. speciosa* analogs need to be evaluated for self-administration in naïve rats. Furthermore, it may also be beneficial to examine these compounds in rodent models of relapse involving the reinstatement model of drug-seeking behavior, as this could provide a translational perspective on potential risk of relapse. Although the findings are promising, the route of administration and doses used in the animal studies may not adequately reflect human consumption. Further studies on physical dependence assessment and self-administration following oral administration in doses comparable to those used by humans are essential to further clarify the magnitude of *M. speciosa* dependence. Despite the positive evidence from animal studies that suggest mitragynine possesses the desired characteristic of candidate pharmacotherapies for opioid dependence and withdrawal, *M. speciosa* or its main derivative mitragynine are still far from being deployed in opioid substitution therapies among patients with OUD in clinical settings. Therefore, well-planned clinical trials are essential to provide unequivocal evidence on the clinical use of *M. speciosa* or its derivatives for OUD. If *M. speciosa* or its alkaloid mitragynine proves to be effective in reducing opioid addiction during chronic treatment and continues to have minimal abuse and dependence liabilities and other unwanted side effects in clinical studies, it could be useful for the development of a new opioid substitution therapy.

AUTHORS' CONTRIBUTIONS

NH, ISJ, RAJ, and FWS wrote the first draft of the manuscript. ZH and MS revised and commented on the manuscript. All the authors contributed to and have approved the final manuscript.

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