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Mitragyna speciosa: Balancing Potential Medical Benefits and Abuse

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ABSTRACT: *Mitragyna speciosa*, also known as kratom, has the potential meet the need for pain medications that lack the addictiveness and overdose risk of classical opioid analgesics, such as morphine. This need is urgent because opioid addiction and overdose deaths have risen throughout diverse segments of U.S. society. Some opioid addicts have found relief in kratom preparations. The use of kratom as an analgesic has been validated by historical accounts and contemporary pharmacological research. Although kratom is a promising source of analgesic candidates, it is a euphoriant with potential for both abuse and addiction. However, kratom appears to be less addictive and to have milder withdrawal symptoms than opioid drugs. Thus, there is a need to balance the potential medical benefits and abuse of *M. speciosa*.

In the U.S., 52,404 people died from drug overdoses in 2015, and drug overdose deaths in 2016 are estimated to have increased 19% to over 59,000.[1] This troubling increase in drug overdose deaths arises predominately from opioid addiction. The path to addiction for both recreational drug users and patients in need of pain management often begins with using prescription opioid painkillers before turning to heroin, fentanyl, and other opiates. Carfentanil, an elephant tranquilizer 5,000 times stronger than heroin, caused 140 drug overdose deaths in Akron, OH in 2016. Opioid addiction has spread throughout the U.S. population regardless of age or profession.

To wean themselves off of morphine and other opiates, to decrease tolerance, or to alleviate opiate withdrawal symptoms, some people turn to preparations of *Mitragyna speciosa*, which is known by several names including kratom.[2,3] Although anecdotal reports suggest that kratom has helped many people overcome opiate addiction and manage pain, others use kratom recreationally to experience its euphoric and sedative effects. Because of these downsides, Thailand banned kratom in 1939 and Malaysia banned kratom in 2004. In the U.S., Alabama, Arkansas, Indiana, Tennessee, Vermont, and Wisconsin banned kratom, and it is on the DEA's list of Drugs and Chemicals of Concern. On August 31, 2016, the DEA issued a notice of intent to temporarily schedule known psychoactive components of kratom, mitragynine, and 7-hydroxymitragynine into schedule I with drugs like heroin, LSD, and marijuana.[4] The structures of mitragynine (**1**) and 7-hydroxymitragynine (**2**) are shown in Figure 1. A ban on mitragynine and 7-hydroxymitragynine would effectively ban kratom because mitragynine is the most abundant alkaloid in kratom leaves (12% in Malaysian *M. speciosa* and 66% in Thai *M. speciosa*).[5]

The DEA's notice of intent argues, "Available data and information for mitragynine and 7-hydroxymitragynine indicate that these substances have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision."[4] This argument overstates the potential for abuse and understates the analgesic and antidepressant uses of kratom. Nearly 150,000 people signed a petition asking for reconsideration of the DEA's notice of intent.[6,7] Kratom proponents argue that, compared to opiates, there is less risk of developing addiction, milder withdrawal symptoms, and no threat of accidental overdose. This argument is supported by decades of research.[2,3,5]

Further studies on the analgesic effects of kratom may reveal new pain medicines that have even fewer adverse effects.[8] In the meantime, rather than banning kratom, conditions for safe use of kratom ought to be vigorously pursued.

■ ETHNOBOTANY

M. speciosa Korth is a native Southeast Asian tree in the same family as coffee, *Rubiaceae*. Historically, Southeast Asian laborers chewed kratom leaves, drank kratom tea, or smoked kratom to increase endurance while farming under the hot sun.[9] Kratom has also been used as a wound poultice, to treat fever, and to suppress opiate withdrawal syndrome.[5] However, at higher doses, kratom induces an opiate-like "high" and impairment, and has been abused as an opium substitute. Kratom addicts display symptoms including skin discoloration, constipation, and weight loss.[9] Withdrawal from kratom is milder than withdrawal from opiates, with symptoms such as irritability, rhinorrhea, insomnia, lachrymation, and lethargy,[2] which have collectively been likened to withdrawal from coffee.[7]

Despite these disadvantages, the most significant advantage of kratom is that it has not caused any overdose deaths. Kapp et al. reported an instance in which a young man developed jaundice and pruritus after taking unusually large doses of kratom in orange juice for 2 weeks.[10] The CDC reported a kratom-related death that involved coconsumption of paroxetine and lamotrigine.[2,6] Overall, both historical and contemporary accounts indicate that the potential benefits of kratom to opiate addicts outweigh the risks.

To date, no compound has demonstrated analgesic effects as effective as the whole leaves.[7] Of the compounds isolated from kratom, mitragynine pseudoindoxyl (**3**), 7-hydroxymitragynine (**2**), and mitragynine (**1**) exhibit analgesic effects comparable to morphine. Although much progress has been made in understanding the pharmacology of such compounds, further research is needed to (i) understand their mechanism of pain/

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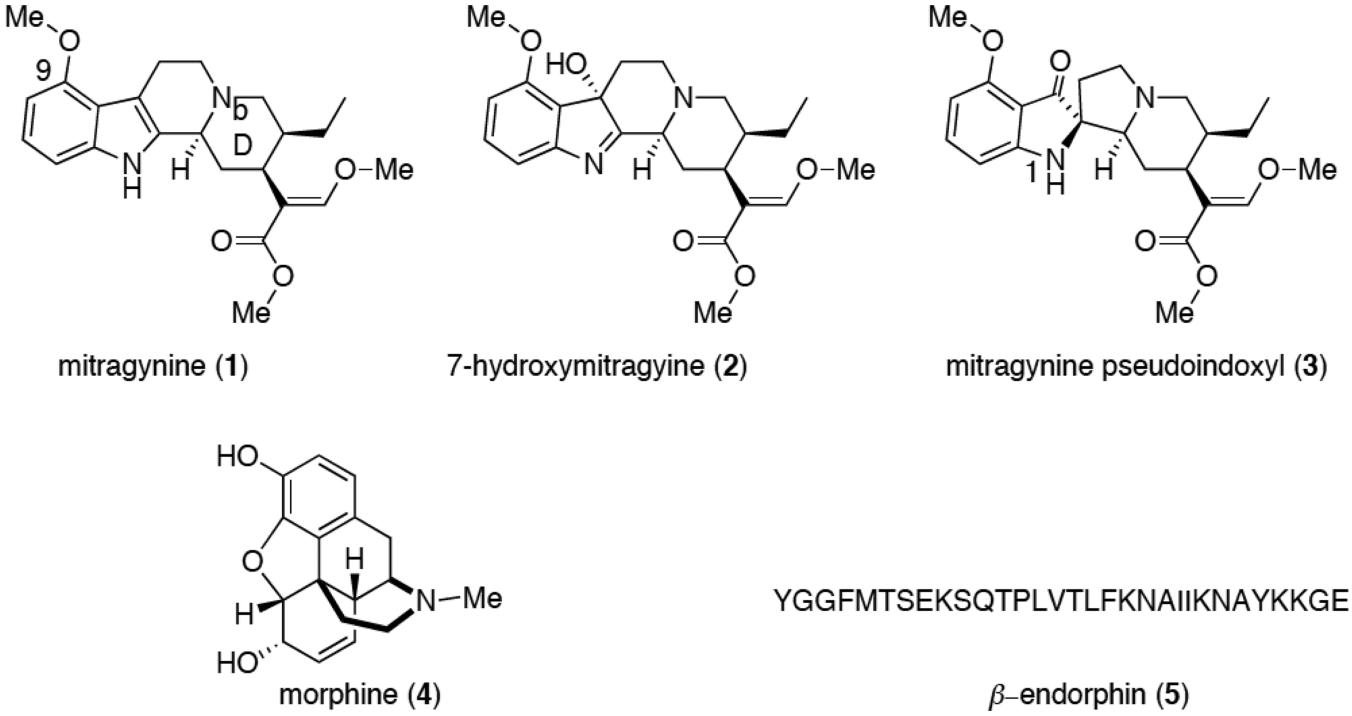

Figure 1. Chemical structures of mitragyna alkaloids, morphine, and amino acid sequence of β-endorphin.

depression relief and (ii) identify compound(s) with diminished adverse effects.

PHARMACOLOGY OF KRATOM INDOLE ALKALOIDS

In the 1960s, several indole alkaloids and Corynanthe-type alkaloids were isolated from *M. speciosa*.[9] Since then it has been known that the alkaloid profile varies in leaves taken from different locations.[5] Within the same plant, the alkaloid profile is different in the flowers, berries, and leaves, and even leaves of different maturity.[12] Smith, Kline, and French Laboratories carried out preclinical trials on mitragynine in humans, but the studies were presumably abandoned after unacceptable side effects (likely nausea and vomiting) were observed.[2,9]

In the 1990s and 2000s, Takayama and co-workers studied the biological activities of crude *M. speciosa* extracts, mitragynine, 7-hydroxymintragynine, and several mitragynine derivatives.[5] Analgesic potency relates to a compound's activity on the ileum. Takayama et al. showed that mitragynine inhibited electrically stimulated contraction in guinea pig ileum preparations, having one-fourth the potency of morphine. Speciociliantine was 13-fold less potent than mitragynine. Speciogynine and payantheine inhibited twitch contraction via direct stimulation of muscarine receptors on ileal smooth muscle. 7-Hydroxymitragynine was 13-fold more potent than morphine and 46-fold more potent than mitragynine. Mitragyna pseudoindoxyl was 100-fold and 20-fold higher than mitragynine and morphine, respectively.

In view of these results, 7-hydroxymitragynine and mitragyna pseudoindoxyl were tested for antinociceptive activity in mice using the tail-flick and hot plate tests. In contrast with the relative potencies of these compounds at inhibiting contraction in the guinea pig ileum assays, the antinociceptive activity of 7-hydroxymitraginine was greater than that of morphine, which was greater than the antinociceptive activity of mitragyna pseudoindoxyl.

Building on this body of knowledge, in 2016, Kruegel and Gassaway et al. of the Sames group studied the activity of mitragynine, 7-hydroxymitragynine, paynantheine, speciogynine, and speciociliatine in HEK cells expressing human μ-opioid receptor (MOR), κ-opioid receptor (KOR), and δ-opioid receptor.[11] Their studies showed that mitragynine and 7-hydroxymitragynine were both partial agonists of MOR, 7-hydroxymitragynine being the stronger agonist. Other major kratom alkaloids, paynantheine, speciogynine, and speciociliantine, were both weak antagonists of MOR. Both mitragynine and 7-hydroxymitragynine were competitive antagonists of KOR. Analogous assays using mouse and rat opioid receptors were similar only for 7-hydroxymitragynine. In mouse MOR, mitragynine was found to be a competitive antagonist. These results suggest that use of rodent models for developing human analgesics may "not be easily translatable to humans."

Additionally, the Sames group demonstrated that mitragynine is a "biased" MOR agonist because it activates GPCR, but not β-arrestin. Such compounds are of interest as analgesics because silencing the β-arrestin pathway decreases undesirable side effects including respiratory depression, constipation, and tolerance. In contrast, morphine (**4**) and β-endorphin (**5**) are balanced MOR agonists that activate both GPCR and β-arrestin pathways.

To further investigate mitragynine activity at human MOR, mitragynine derivatives were synthesized. Substitution of the methoxy group at position 9 with a hydroxyl group exhibited similar potency to mitragynine. Removing the enol ether from the β-methoxyacylate moiety eliminated both agonist and antagonist activity at human MOR. However, (*Z*)-mitragynine retained activity similar to mitragynine. Removal of the ethyl group on ring D decreased agonist activity. In sum, the enol ether of the β-methoxyacylate and the ethyl group on ring D appear to be key structural features of mitragynine. Finally, (+)-mitragynine, the unnatural enantiomer of (−)-mitragynine,

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exhibited decreased MOR activity and switched from an antagonist to weak agonist at KOR.

These findings complement Takayama's structure−activity relationship studies in guinea pig ileum, which generally showed that modification of the group at C9 and the β-methoxyacylate moiety decreased potency compared to mitragynine.[5] Corynantheidine is a functional opioid antagonist, and 9-hydroxycorynantheidine is a partial agonist, which suggests that the C-9 methoxy group is functionally important to mitragynine opioid agonism. The N_b oxide exhibited no agonistic activity, indicating at the N_b nitrogen is also essential to opioid activity.

Váradi et al. demonstrated that mitragynine pseudoindoxyl and C-9 substituted derivatives thereof are MOR agonist/DOR antagonists *in vitro*.[8] Mitragyna pseudoindoxyl displayed the highest binding affinity to murine MOR and DOR and moderate affinity for KOR. 7-Hydroxymitragynine showed moderate affinity at the MOR, which was 5-fold greater than that of mitragynine. Mitragyna pseudoindoxyl C-9 derivatives (−H, −OH, −CN, −Ph, −furan-3-yl, −OAc) generally maintained MOR and DOR affinity, but substitution at the N-1 (−benzyl, −Me) position eliminated opioid affinity. These results suggest that the indole NH is important for receptor binding. These binding affinities are consistent with the observed MOR agonism and DOR antagonism. Notably, these derivatives also exhibited biased MOR agonism and did not recruit β-arrestin-2.

In mice, using the radiant heat tail-flick assay, the three major alkaloids exhibited potent analgesic activity and milder side effects than morphine. Subcutaneously administered mitragynine was 66-fold less active than morphine. Mitragynine pseudoindoxyl was 3-fold more potent than morphine, and 7-hydroxymitragyinine was 5-fold more potent than morphine. Advantageously, mitragynine pseudoindoxyl caused less tolerance, respiratory depression, and inhibition of gastrointestinal motility than equianalgesic doses of morphine.

Mitragynine pseudoindoxyl also appears to lack addictiveness because it did not produce conditioned place preference or aversion in mice. An earlier study showed that mice developed conditioned place preference for the site of 7-hydroxymitragynine administration.[3] Therefore, the pharmacological profile of mitragynine pseudoindoxyl appears to be superior to that of 7-hydroxymitragynine.

As a whole, this research suggests that kratom is a promising source of analgesic candidates, though this assertion awaits confirmation in human subjects. Data also suggest that kratom has the potential to prevent opioid overdoses, a rising killer in diverse segments of the U.S. population. While research on kratom and its alkaloids continues, strategies for preventing and managing kratom addiction should be developed. Additionally, testing and labeling requirements should be implemented to inform consumers of alkaloid contents and to protect consumers from adulterated products. Along these lines, photochemical oxidation of mitragynine in air yields 7-hydroxymitragynine,[11] suggesting that storage conditions can affect potency.[12] This points to a need for quality control measures to protect consumers. These opportunities to develop and promote safe *M. speciosa* use protocols should be embraced.

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Notes

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