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Review Article

Assessing the Impact of Kratom (*Mitragyna speciosa*) on Prenatal and Maternal Outcomes: Pharmacological Insights and Health Hazards

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Abstract

Use and misuse of kratom (*Mitragyna speciosa*), a Southeast Asian plant with both medicinal and psychoactive properties, has recently seen a significant rise in uncontrolled use. Due to the increased use and the abuse potential, this review provides a snapshot of the pharmacological properties and the dangers associated with kratom. Additionally, this review will help highlight a gap in our understanding of kratom use among pregnant women. The increase in opioid use in general has led to a growth in infants with neonatal opioid withdrawal syndrome (NOWS). However, only a handful of NOWS cases have been reported with kratom users. Currently, there is little to no evidence about the short- and long-term effects on neonates born with NOWS due to kratom abuse by mothers. In addition, very few animal models exist for the effects of kratom on adults and infants. This review suggests the need for further research and immediate interventions to safeguard the well-being of pregnant mothers and infants exposed to kratom in utero.

Keywords: *Kratom; Mitragynine; Neonatal; Abuse; Opioid; Withdrawal*

Abbreviations

US: United States; NSDUH: National Survey on Drug Use and Health; FDA: Food and Drug Administration; NOWS: Neonatal Opioid Withdrawal Syndrome; MTG: Mitragynine; 7-OHMG: 7-Hydroxy Mitragynine; MOR: μ-Opioid Receptors; KOR: κ-Opioid Receptors; DOR: δ-Opioid Receptors; CYP: Cytochrome P450; NPS: Novel Psychoactive Substances; NIDA: National Institute on Drug Abuse; CDC: Centers for Disease Control and Prevention

Introduction

Kratom originates from a native tropical tree known as *Mitragyna speciosa* Korth, of the Rubiaceous family, found within Southeast Asia, the Philippines, and New Guinea. The plant thrives in warm environments (20-30 degrees celsius) with a soil pH between 5.5-6.5 and well-balanced sun exposure [1]. The leaves from *M. speciosa* are dried, fermented, and ground into a powder to make kratom [2]. Historically, kratom has been used for therapeutic reasons to treat conditions such as muscle pain, diabetes, intestinal infections, coughing, and diarrhea [3-6]. There are reports of kratom having been used to treat opium addiction and for the detoxification of morphine-addicted patients in Malaysia and Thailand, respectively [7].

Over the past decade, kratom has become widely available on the internet and in person, and its use for "self-treatment" as a substitute for alcohol, opioids, and stimulants has grown in the United States (US) [8,9]. Recent developments in kratom studies and surveys completed in the US indicate kratom is commonly used to manage pain, coughing, anxiety, diarrhea, depression, and opioid withdrawal [10]. In an online survey of kratom users (n = 2867), 48.4% primarily use kratom for pain relief [10]. Furthermore, a double-blind lab-based study discovered a significant increase in pain tolerance one hour after kratom consumption [11]. Additionally, kratom has been shown to decrease alcohol abuse [9]. An anonymous survey conducted between January 2021 and May 2021 (n = 80), of pregnant and postpartum individuals with substance use disorders discovered that 32.5% of individuals used kratom primarily to relieve opioid withdrawal symptoms, control pain, and reduce stress [12]. Individuals with a history of substance use disorder commonly describe taking kratom to help manage their withdrawal symptoms associated with opioid addiction [9,13-16]. However, these above-highlighted reasons are not approved uses of kratom. Table 1 summarizes the proposed therapeutic indications of kratom.

Indications	Types of Evidence		
	Rodent Model	US Self-Report Online Survey	Southeast Asia Self-Report Survey
Analgesia	Y	Y	Y
Fatigue	N/A	Y	Y
Opioid withdrawal	Y	Y	Y
Opioid use disorder	Y	Y	Y
Alcohol withdrawal	Y	N	N
Alcohol use disorder	Y	N	N
Stimulant use disorder	N	Y	N
Anxiety	Y	Y	Y
Depression	Y	Y	Y
Psychosis	Y	N	N

Table 1: *Summary of the proposed therapeutic indications of kratom [10,13,26,66,77,78].*

N = No Evidence; Y = Yes, Supported by Evidence; N/A = Not Applicable or Not Available.

Kratom has been highly reported to be co-administered with agents such as opioids, benzodiazepines, and over-the-counter Tylenol® [17,18]. The 2019 US National Survey on Drug Use and Health (NSDUH) discovered that kratom use was closely associated with the abuse of cocaine (adjusted odds ratio 1.60 [95% CI 1.06-2.69]), nonmedical prescription use of stimulants (adjusted odds ratio 2.10 [95% CI 1.44-3.05]) prescription opioid use disorder (adjusted odds ratio 3.20 [95% CI 1.38-7.41], and use of cannabis (adjusted odds ratio 4.57 [95% CI 3.29-6.35]) [18,19]. In 2021, NSDUH concluded that 1.7 million Americans aged 12 years and older used kratom in the past year. There exists a discrepancy between sources about the estimated number of kratom users, however, the general trend suggests an increase in use [14,19-21]. Based on data provided by kratom marketers regarding imports and sales, it is estimated that there are approximately 3 to 5 million adult consumers [19,20]. Additionally, a recent analysis of the US Food and Drug Administration (FDA) adverse events reporting system from January 2004 to September 2021 revealed the average age of patients with kratom-related adverse reactions was 35.5 ± 11.5 years [22].

Despite increasing evidence of kratom's use and potential toxicities, the FDA has yet to approve any uses for this substance. The World Health Organization's 2021 report states that kratom is not regulated under international UN treaties, and their expert committee on drug

dependence did not recommend continuous surveillance of kratom, though no critical review was provided [23]. Consequently, the safety and purity of kratom remains unregulated. Moreover, kratom, along with other novel psychoactive substances, is not routinely included in health histories taken by clinicians [24], resulting in its use remaining largely undetected and unmonitored.

The ambiguity surrounding kratom use persists, with some case reports and studies indicating minimal risk, while others highlight significant dangers. The rise in kratom use and abuse is primarily attributed to its unregulated status and widespread availability in tobacco and smoke shops [5,25]. A major concern is the availability of kratom on the internet and dark web, where misleading advertisements claim it is non-addictive and a safer alternative to opioids [26,27]. A January 2023 study evaluating the reliability and quality of information provided by kratom vendors found that while vendors generally provide accurate information about product quality, their information on potential adverse effects and dangers is inadequate [28]. The health benefits claims made online and in stores by kratom vendors are concerning and potentially dangerous as they lack rigorous research support. This gap in research combined with unsupported internet claims underscores the need for more rigorous studies on kratom's medical use, toxicity, and side effects.

Additionally, as noted, kratom use among pregnant women has resulted in cases of neonatal opioid withdrawal syndrome (NOWS) [24]. Although research on kratom's pharmacological and toxicological effects is increasing, which may aid in educating both consumers and health professionals, evaluating adverse health outcomes related to kratom use alone remains challenging due to its common combination with other substances. Furthermore, there is a continuing lack of data on kratom use during pregnancy and its impact on neonatal development.

Discussion

Pharmacological properties of kratom

Kratom is biologically and structurally different from classic opioids, classifying it as an atypical opioid [29]. The chemical composition of kratom varies by its leaf vein colors-red, white, green, or yellow [2]. It is an herbal product that can produce both opioid-like and stimulant-like effects. Until recently, it was estimated that approximately forty indole alkaloids were present in the leaves of *Mitragyna speciosa*, exhibiting either synergistic or antagonistic pharmacological interactions [30,31]. However, some studies in 2023 identified more than 50 metabolites [32]. In addition to alkaloids, kratom leaves contain terpenes, flavonoids, and polyphenols [33,34].

Two of the major alkaloids in kratom, mitragynine (MTG) and 7-hydroxy mitragynine (7-OHMG), play significant roles in its pharmacological and psychoactive effects [35-38]. Of the indole-based alkaloids, MTG makes up approximately 66%, while 7-OHMG makes up about 2% [35-37]. Although other alkaloids may also contribute to kratom's effects, MTG and 7-OHMG are the most well-studied [30,34,39].

Studies have shown that MTG and 7-OHMG act as G protein-coupled receptor agonists at the μ-opioid receptors (MOR). However, these compounds produce minimal activation of the β-arrestin intracellular pathway [30,31,40]. This selectivity minimizes adverse effects typically mediated by the β-arrestin pathway, such as respiratory depression or physical dependence [38]. Kratom's effects, which onset within minutes and last for a few hours, are dose-dependent: it acts as a stimulant at lower doses, exhibits opioid-like euphoric effects at higher doses, and causes sedation at extremely high doses [2,11,41].

Several pharmacological experiments have demonstrated that MTG and 7-OHMG have variable effects on MOR, with both alkaloids exhibiting antagonistic effects on κ-opioid receptors (KOR) and δ-opioid receptors (DOR) [37,42,43]. The binding affinities of MTG and 7-OHMG to MOR (Ki = 709 and 77.9 nM, respectively) were higher compared to their affinities for KOR or DOR; for instance, MTG's binding affinity to MOR (Ki = 709 nM) is much lower than that of opioids such as fentanyl (Ki = 7.96 nM), morphine (Ki = 4.19 nM), and naltrexone (Ki = 1.84 nM) [40]. However, 7-OHMG shows a binding affinity to MOR that is 9.1 times greater than that of MTG [40].

Obeng., *et al*. also found that MTG exhibits minor antagonist effects *in vitro* but low agonistic efficacy *in vivo* [40]. Inconsistencies in MTG's efficacy across studies may be attributed to variations in MOR expression profiles between species used in these studies (e.g. human vs. rodent). Overall, the study concluded that MTG demonstrates low affinity for MOR and exerted both agonistic and antagonist activity depending on the assay used [40]. Understanding the MOR-specific efficacy of MTG and 7-OHMG is essential in determining the therapeutic benefits and potential adverse effects of kratom. Clinically, the safety and efficacy of opioids are reciprocally related. Table 2 provides a summary of kratom's opioid receptor binding affinities relative to MTG, while figure 1 illustrates the cellular G-protein- and β-arrestin-mediated mechanisms following the binding of kratom's major alkaloids to MOR, along with associated physiological effects.

Alkaloid	Present in Kratom leaf	Opioid Receptor Specific Binding Affinity		
		MOR	DOR	KOR
Mitragynine (MTG)	Y	1	1	1
7-OH-mitragynine (7-OHMG)	Y	5 - 20	11 - 80	2 - 10
MTG pseudoindoxyl	Y	300	300	10
Morphine	N	50 - 150	>50	10 - 30
Buprenorphine	N	200	>1000	700 - 1000

Table 2: *Summary of the opioid receptor binding affinities for kratom alkaloids and opioids relative to mitragynine [40,42,79].*

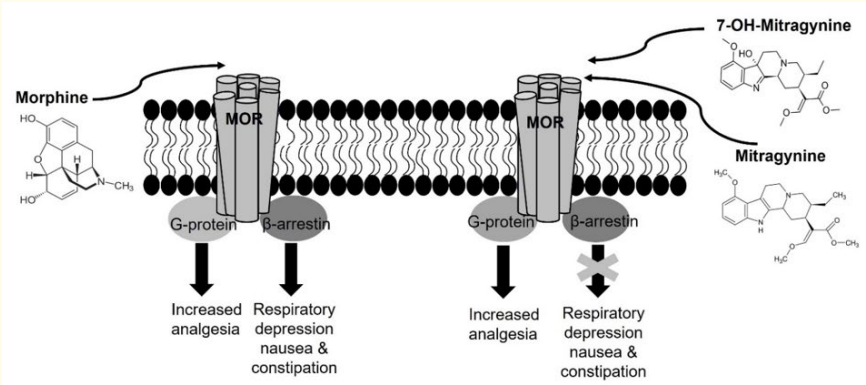

Figure 1: *The cellular G-protein and β-arrestin mechanisms following binding of major alkaloids of kratom to the MOR and associated physiological effects.*

MTG and 7-OHMG also exhibit activity at adrenergic (α1 and α2), serotonin (1A and 2A), and dopamine (D1) receptors [31,44,45]. The significance of this receptor binding in relation to kratom's effects remains unclear. For example, stimulation of α2-adrenergic receptors by MTG can result in sedation and hypnotic effects without leading to respiratory depression [46,47]. Although data is lacking, it is possible that kratom's non-opioid receptor effects may have therapeutic potential in opioid withdrawal therapy.

Kratom also inhibits several cytochrome P450 (CYP) enzymes, including CYP2D6, CYP2D9, CYP1A2, and CYP3A4 [36,48,49]. This inhibition or induction of CYP enzymes and P-glycoproteins makes combining kratom with substances such as alcohol, anticonvulsants, opioids, and muscle relaxants particularly dangerous [25,49].

Dangers associated with the use of kratom

Consumers have self-reported that using kratom to treat opioid addiction reduces their experience of classic withdrawal symptoms [50]. However, the chronic use, abuse, and cessation of kratom are problematic due to its adverse effects. In addition to the pharmacological dangers previously discussed (e.g. potential toxicities, interaction with CYPs), several case studies highlight opioid-like withdrawal syndrome from psychological or physical addiction associated with uncontrolled kratom use [51-53]. A cross-sectional survey study of regular kratom users (n = 293) in Malaysia concluded that 45% of users developed moderate kratom dependence [15]. Withdrawal symptoms from kratom use include rhinorrhea, arthralgias, myalgias, hostility, inability to work, jerky motions of limbs, depression, and mild anxiety [16,54]. There are currently only a handful of cases that can provide guidance on how to treat withdrawal symptoms due to kratom abuse [50,55-57]. Treatment protocols employed buprenorphine-naloxone, clonidine, hydroxyzine, or some mixture of these to relieve the symptoms associated with kratom abuse and/or withdrawal [51,52,58,59].

The number of kratom exposures reported to poison control centers in the US is rising [17,60]. Alarmingly, between 2011 and 2017, kratom use increased by 4,948.9% [60], and the CDC has reported that more than 90 deaths were attributed to kratom use between 2016 and 2017 [61]. The United States poison control reported approximately 67,369 calls for novel psychoactive substances (NPS) like kratom between 2000 to 2017 [60]. Between 2010 and 2015, 428 calls regarding kratom use were made to healthcare providers and 660 calls were made to US poison control centers [17]. In fact, of the four leading substances reported to US poison control, kratom had the highest rates of dangerous medical outcomes and hospitalizations [60].

Kratom and neonatal opioid withdrawal syndrome (NOWS)

According to survey data from the National Survey on Drug Use and Health (NSDUH) and the National Institute on Drug Abuse (NIDA), many women of childbearing age use opioid treatment to manage pain [62]. Additionally, women often respond differently to drugs and are prescribed treatments that have not fully been tested on women (NIDA 2022). During labor and delivery between 1999 to 2014 opioid use disorder by women quadrupled (NIDA 2020) [63]. A 2019 analysis by the Centers for Disease Control and Prevention (CDC) found that 6.6% of women self-reported opioid use during pregnancy [64]. This is concerning due to the potential effects on the fetus and neonate. A 2017 US study determined that for every 1,000 newborns who stay in the hospital, seven were diagnosed with NOWS [65]. These numbers warrant a discussion about novel opioids like kratom and their short- and long-term effects on infants.

The prevalence of kratom use among pregnant women is unknown. However, its use is growing in the US due to its marketing as an alternate opioid for mental health concerns such as depression and anxiety [24]. It is also marketed to reduce opioid withdrawal symptoms [8-10,50,66]. The rise in kratom use and the lack of comprehensive understanding of its effects are dangerous. Accordingly, a systematic review recommended that pregnant women avoid using kratom due to insufficient data [48]. A recent systematic review by Wright., *et al*. examined the limited case studies on kratom use during pregnancy and its effects on mothers and infants [24]. Five infants discussed by Wright., *et al*. had gestational ages between 37 weeks to 5 days; all except one were diagnosed with NOWS, with one infant having a Finnegan score of 18 before treatment; and the infants diagnosed with NOWS were treated with a morphine-weaning protocol [24]. Mothers experienced withdrawal symptoms such as anxiety, restlessness, diaphoresis, and piloerection [24]. The study emphasized the need for further understanding of maternal symptomatology and many other factors. Additionally, a few published studies have associated the use of kratom to treat pain, anxiety, or opioid withdrawal during pregnancy with NOWS [67-70]. A recent case report noted that severe NOWS associated with maternal kratom use could be treated using oral phenobarbital [71].

Animal studies, NOWS, and future possibilities

A study exposed its zebrafish embryos to mitragynine, speciociliatine, and morphine for 96 hours post-fertilization [72]. Several physical factors, such as morphological malformations, heart rate, and mortality, were measured. Damodaran., *et al*. concluded that

kratom alkaloids caused morphological modifications, scoliosis, and death at 100 µg/ml. Although this study highlighted teratogenic risks during pregnancy, significant gaps remain in understanding the long-term and short-term effects of maternal kratom use on the development of infants with NOWS.

Conclusion

Kratom's increasing availability and corresponding rise in abuse have fueled ongoing debate ongoing about the need for further research in both preclinical and clinical settings and FDA regulation. Rigorous human clinical trials of kratom as a potential alternative to pain control are necessary before making any recommendations for its medical use. Current human studies on kratom are observational surveys from Malaysia and Thailand [11,54]. Understanding novel psychoactive substances like kratom is essential because opioid use disorders affect over 3 million individuals in the US with 109,360 drug overdose deaths occurring in 2022, placing a substantial burden on our healthcare system [73,74].

While several questions remain unanswered about kratom, this review has highlighted key research and current gaps important to educating healthcare providers and consumers about this drug. The most pressing issue today is understanding kratom's safety profile, enabling consumers and healthcare providers to better manage the risks associated with its unregulated use. A particular area of concern is the use of kratom during pregnancy, an inherently challenging demographic in which to study the adverse effects of drugs. Understanding how drugs affect the fetus and neonates is crucial for developing prevention strategies to provide optimal care for childbearing mothers.

Since the announcement of plans to classify kratom and its MTG constituents as Schedule I Controlled substances by the US Drug Enforcement Administration [75], there has been substantial debate regarding the benefits and safety of kratom. Proponents argue that kratom is safer and less addictive for pain management and opioid addiction than other opioids. The use, availability, and media attention have intensified recently, making it imperative for physicians, researchers, and policymakers to be knowledgeable about kratom. However, further research is needed to achieve this.

Most information about the pharmacodynamics and pharmacokinetics of kratom in humans comes from retrospective self-report surveys of kratom users. Further research could entail assessing withdrawal behavior in a preclinical model of NOWS to understand the short-term effects of prenatal morphine. For example, our research team has characterized a preclinical model of NOW using a novel mouse species [62]. Spiny mice have been identified as optimal for NOWS research due to their brain development closely resembling human patterns [62,76]. This preclinical model could help us better understand the effects of maternal kratom use on prenatal development.

The goal is to answer questions such as: (1) can kratom be used as therapy for NOWS, (2) what are the short- and long-term effects of kratom use on brain development, inflammation, and overall neonatal development, and (3) how does kratom use affect short- and long-term memory and cognition?

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