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Kratom (*Mitragyna speciosa*): Medicinal Marvel or Menace? Assessing Potency, Risk, and Future Prospect of Herbal Medicine

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Abstract

Kratom (*Mitragyna speciosa*) boasts a rich historical legacy as an herbal plant employed across generations for diverse therapeutic purposes, including pain relief, inflammation mitigation, anti-diarrheal effects, cough suppression, alleviation of fatigue, and anti-anxiety and antidepressant properties. Despite its acclaimed medicinal versatility, this plant harbors psychoactive attributes, thereby posing the risk of misuse and potential dependence, along with withdrawal effects. The alkaloid composition of kratom, featuring opioid receptor agonist properties, underscores its analgesic efficacy, thereby carrying a risk of dependence and withdrawal akin to other opioid agonists. Beyond its role as an opioid agonist, the analgesic mechanism of kratom extends to additional complementary pathways, presenting a potential superiority to morphine. Notably, kratom constituents inhibit key drug-metabolizing enzymes (CYP) and the multidrug transporter, p-glycoprotein, potentially leading to heightened levels of co-administered drugs that are substrates for these proteins, presenting a potential risk of adverse outcomes, including fatality. Given the perceived imbalance of risks versus benefits, there arises a rationale for the prohibition of kratom use as an herbal remedy. However, the exploration of purified drugs derived from kratom isolates remains a promising avenue for research, with the potential to surpass standard pharmaceutical interventions.

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Introduction

Kratom (*Mitragyna speciosa* Korth.) is a psychoactive plant widely distributed in Southeast Asia, such as Thailand, Malaysia, and Indonesia. It belongs to the coffee family, Rubiacea. In Indonesia, it can be found in Borneo, along the Kapuas River basin (Novindriani et al., 2022). Kratom has long been used mainly for two reasons: health purposes and recreational use. For medicinal properties, kratom has the benefit of addressing minor health issues, such as pain, fever, diarrhea, diabetes, wound care, antitussive, antidepressant, anxiolytic, and stimulant to increase work efficiency, endurance, tolerance to hot and humid climate conditions, and treat morphine's withdrawal symptom (Harahap et al., 2022; Trakulsrichai et al., 2015; Veltri & Grundmann, 2019). At lower dosage ranges (1-5 g), kratom exhibits stimulatory effects akin to those observed with cocaine or methamphetamines. Conversely, at elevated doses, kratom is correlated with the induction of euphoria, analgesia, and sedation.

In recent times, a younger demographic has adopted the use of kratom tea as a foundational element for a concoction called "4x100," which combines kratom tea with cough syrup (containing codeine and/or diphenhydramine), Coca-Cola, and ice cubes. This trend has raised concerns due to the incorporation of additives like benzodiazepines to amplify the effects (Meireles et al., 2019). Dried kratom leaves can be used as cigarettes to provide a relaxing effect.

In Indonesia, the resurgence of kratom's popularity followed a controversial statement by the Minister of Home Affairs expressing support for the export of kratom as an herbal plant. Prior to this, Indonesia held the distinction of being the largest exporter of kratom to the United States, primarily in the form of simplicial powder (Henningfield et al., 2022). Concurrently, within Indonesia, the regulation of kratom falls under the purview of the National Agency of Drug and Food Control (NA-DFC), as outlined in Circular No. HK.04.4.42.421.09.16.1740 of 2016. This circular pertains to the prohibition of the use of *Mitragyna speciosa* (Kratom) in registered traditional medicines (Harahap et al., 2022). However, the regulation pertaining to individual consumption remain unregulated. Therefore, this review article endeavors to expound upon both the benefits and risks associated with kratom usage as traditional medicine. The elucidation of these facets serves as a crucial consideration for governmental deliberations regarding the liberalization or restriction of kratom use in Indonesia.

Phytochemical Content and Pharmacological Activities

Kratom leaves contain alkaloids, flavonoids, triterpenoid, saponin, tannin, and glycoside derivatives (Yuniarti et al., 2020). Alkaloids are considered as the main contributor of its pharmacological effect. At least there are 10 alkaloid compounds identified from kratom leaves. The major constituent of alkaloid is mitragynine, contributing to 66% from total alkaloid (Ƶ.Hassan et al., 2013). The second essential alkaloids are speciogynine and paynantheine, contribute to 16% of total alkaloid (Chear et al., 2021). The rests are corynoxine, corynoxine B, isospeciofoline, mitragynine oxindole B, hydroxymitragynine, corynantheidine, speciociliatine, and speciociliatine N(4)-oxide. The presence of distinct alkaloids in each *M. speciosa* plant seems to be primarily influenced by their source and environmental conditions, including climates, soil types, and environmental pressures. (Chear et al., 2021).

Among the 10 alkaloid compounds subject to investigation, a subset has been identified as possessing opioid-like properties, notably including mitragynine, hydroxymitragynine, speciociliatine, corynantheidine, and corynoxine (Chear et al., 2021; Kruegel & Grundmann, 2018). Similar to conventional opioids, these compounds exhibit the capacity to bind to opioid receptors, thereby inducing effects akin to morphine, such as analgesia. Opioid receptors are classified into 5 types: μ, κ, δ, and nociception/orphan receptor (NOR), and ζ receptors (Pawar et al., 2017). Relative to other alkaloids, corynoxine demonstrates the highest affinity for the μ-opioid receptor, although its binding affinity remains lower than that of standard opioids such as morphine. In vitro studies indicate that corynoxine is less potent than morphine, with a fourfold higher inhibitory constant. Paradoxically, in vivo studies reveal a different outcome, with the ED50 value of corynoxine being 6.75 mg/kg, half that of morphine's 12.1 mg/kg (Chear et al., 2021).

Mitragyinine and its metabolite, 7-hydroxymitragynine are other alkaloids of kratom studied extensively. In comparison to mitragynine, 7-hydroxymitragynine demonstrates notably higher affinity for opioid receptors. Specifically, it exhibits approximately 5-14 times greater affinity at the μ-opioid receptor, 4 times at the κ receptor, and 70 times at the δ receptor compared to mitragynine (Váradi et al., 2016). In contrast to morphine, both compounds may function as partial μ receptor agonists and δ receptor antagonists (Kruegel & Grundmann, 2018). Despite their partial agonistic nature, both mitragynine and 7-hydroxymitragynine demonstrate greater potency in terms of analgesic activity than morphine. In antinociception assays, 7-hydroxymitragynine exhibits 40 times greater potency than mitragynine and tenfold greater potency than morphine (Váradi et al., 2016). Their analgesic properties appear not to be confined solely to their μ receptor activity; in a separate study, mitragynine was found to inhibit neurotransmitter release by reversibly blocking neuronal Ca^{2+} channels, suggesting that the decrease in neurotransmitters contributes to the inhibition of pain transduction (Meireles et al., 2019). Kratom

additionally engages in alternative mechanisms, including the activation of noradrenergic and serotonergic pathways in the spinal cord, stimulation of postsynaptic alpha-adrenergic receptors, inhibition of cyclooxygenase-2 (COX-2), and the inhibition of prostaglandin synthesis. Moreover, it modulates the 5-hydroxytryptamine receptor by blocking its stimulation, thereby introducing a multifaceted approach to its analgesic effects (Abdullah et al., 2019). Unlike opioid, kratom may act as inflammatory-induced pain as well.

The question of whether chronic use of kratom leads to dependence remains a subject of conflicting findings. While certain studies assert that chronic kratom use induces dependence (Singh et al., 2019; Suhaimi et al., 2016), there are also reports suggesting that physical pain experienced during kratom cessation is notably more severe in kratom users compared to illicit opioid users (Singh et al., 2019). The prevalence of withdrawal symptoms among users is substantial, with one study revealing that over half of patients regularly consuming kratom for six months or more developed severe withdrawal symptoms upon cessation (Prozialeck et al., 2012).

In contrast to these observations, mitragynine, a component of kratom, is reported not to cause withdrawal symptoms and, in fact, may alleviate withdrawal symptoms associated with morphine (Harun et al., 2020; R. Hassan et al., 2020). A study demonstrated that the combined administration of mitragynine with morphine increased antinociception compared to morphine alone and prevented the development of morphine tolerance (Fakurazi et al., 2013). The discrepancy in withdrawal effects between mitragynine and morphine can be clarified by their respective agonistic properties. Mitragynine functions as a partial agonist, whereas morphine acts as a full agonist. Furthermore, mitragynine sets itself apart by abstaining from recruiting β-arrestin-2 upon binding to the μ receptor, a feature not shared with morphine (Kruegel et al., 2016). This distinctive attribute diminishes the likelihood of inducing dependence and respiratory depression while preserving its analgesic effects(Ya et al., 2019). However, it is crucial to note that the metabolite of mitragynine, 7-hydroxymitragynine, similarly refrains from recruiting β-arrestin-2, leading to physical dependence and potential cross-tolerance to morphine (Hemby et al., 2019). The mechanism behind this should be investigated further.

In addition to its analgesic effect, kratom has demonstrated various pharmacological effects, including antidiabetic, anti-inflammatory, antipsychotic, sedative, antidepressant, anxiolytic, antidiarrheal, antioxidant, and antimicrobial properties (refer to **Table I**). Some of these effects are associated with kratom's opioid activity, while others appear unrelated. As with many herbal plants, predicting the specific effects of kratom can be challenging, as they depend on the phytochemical profile of its contents, particularly its alkaloid composition (Todd et al., 2020). Consequently, unstandardized crude extract of kratom may pose greater risks compared to its isolated components, such as mitragynine.

Table I. The Pharmacological Effects of Kratom

Activity	Materials and dose or concentration	Method	Result
Antidiabetic	Ethanol, methanol, aqueous extract of kratom leaves Mitragynine (Limcharoen et al., 2022)	In vitro: α-glucosidase inhibition	IC_{50} ethanol extract 15.9 ± 1.34 μg/mL IC_{50} methanol extract 42.12 ± 1.76 μg/mL IC_{50} aqueous extract 69.48 ± 2.67 μg/mL Mitragynine 81.68 ± 1.70 μg/mL All of the extract and mitragyinine is more potent than acarbose (IC_{50} 728.20 ± 7.01 μg/mL
	Ethanol extract of kratom leaves with dose of 100 and 400 mg/kgBW (Zhang et al., 2023)	In vivo: Fructose/ streptozotocin-induced DM	Treatment using kratom decrease glucose blood level and increase serum insulin leveland increase insulin expression in diabetic rat
Antinociceptive	Methanol extract with dose of 50, 100, 200 mg/kgBW (Shaik Mossadeq et al., 2009)	In vivo: Acetic acid-induced writhing test	Methanol extract at dose of 100 and 200 mg/kgBW reduce writhing significantly, with % inhibition of 39.6% & and 52.3%, respectively
		In vivo: Formalin-induced pain	Methanol extract at dose of 100 and 200 reduce time spent licking, with % inhibition of 36.2 and 46.3%; lower than morphine (53.9%) but higher than aspirin (29.5%)

Activity	Materials and dose or concentration	Method	Result
		In vivo: Hot plate	At 60 min after induction, latency time of group administered with methanol extract were higher significantly than control
	Aqueous extract, methanol extract, ethanol extract, ethyl acetate extract, with dose of 200 mg/kgBB (Goh et al., 2021)	In vivo: Hot plate	Latency time of jumping and licking of ethyl acetate, ethanol, and methanol extract group are significantly higher than vehicle (ethyl acetate and ethanol $p < 0.001$; methanol $p < 0.01$). Aqueous extract has no analgesia effect. Efficacy of all extracts are less potent than morphine
		In vivo: Tail flick	Latency time of flicking tail of ethyl acetate and methanol group are significantly higher than vehicle (ethyl acetate and methanol $p < 0.001$, ethanol $p < 0.01$), while aqueous extract has no effect
	Mitragynine 7-hydroxymitragynine (Kruegel et al., 2019)	In vivo: Tail flick	ED50 7-hydroxymitragynine subcutaneous 0.6 mg/kgBW ED_{50} mitragynine sc 106 mg/kgBW ED_{50} mitragyinine peroral 2.05 mg/kgBW
	Mitragynine 0 – 10 mg/kgBW(Foss et al., 2020)	In vivo: Oxaliplatin-induced allodynia	Mitragynine 10 mg/kg reduce oxaliplatin-induced allodynia on days 2 and 5 Analgesic effect of mitragynine is inhibited by α-adrenoceptor antagonist and opioid antagonist
	Mitragynine 92, 163, and 293 mg/kg 7-hydroxymitragynine 32, 56, 100 mg/kg (Berthold et al., 2022)	Hotplate	The analgesic activity of mitragynine at a dosage of 293 mg/kg is commensurate with that of 7-hydroxymitragynine at a concentration of 100 mg/kg. However, the duration of pain suppression by mitragynine exceeds that of 7-hydroxymitragynine.
Anti inflammatory	Methanol extract with dose of 50, 100, 200 mg/kgBW (Shaik Mossadeq et al., 2009)	In vivo: Carrageenan-induced paw edema	All doses inhibit edema start from 1 hour after administration
		In vivo: Cotton pellet – induced granuloma test	Extract with dose of 200 mg/kgBW is significantly inhibit edema, with % inhibition is higher than aspirin (44.9% vs 25.4%)
	Mitragynin 0.5, 1, 10, 20 µg/mL (Utar et al., 2011)	In vitro: mRNA expression of COX-2 in LPS stimulated in macrophage cells	Extract with dose of 1-20 µg/mL may significantly inhibit expression COX-2, but not COX-1 Extract with dose of 1 – 20 µg/mL ia able to suppress PGE-2 production
	Methanol extract with dose of 75 mg/kg, 150 mg/kg, and 200 mg/kg(Salim et al., 2022)	Carrageenan-induced paw edema	All doses inhibit edema start from 1 hour after administration
Antipsychotic	Methanol extract (50, 75, 100, 125, 250, 500 mg/kgBB) (Vijeepallam et al., 2016)	Apomorphine-induced climbing behavior	An inverted bell-shaped dose-response relationship is observed in mouse cage climbing behavior, where the extract, administered at doses of 75 and 100 mg/kg, leads to a significant decrease in

Activity	Materials and dose or concentration	Method	Result
			climbing behavior and climbing time. This decline suggests an antipsychotic-like effect, and it is postulated that this effect is mediated through the extract's interaction with the dopaminergic system.
		Ketamine-induced social withdrawal	A bell-shaped reversal response to ketamine-induced social withdrawal in mice has been observed. Significantly, doses of 75 and 100 mg/kg of the extract effectively reversed the social deficit induced by ketamine. This reversal is hypothesized to be mediated through the inhibition of dopamine D2 receptors and serotonin 5HT2A receptors.
Sedative	Ethanolic extract with dose of 971.4, 485.8, and 242.8 mg/kg Infusion with dose of 1950, 3900, and 7800 mg/kg (Novindriani et al., 2022)	Traction test	Both extract and infusion at medium and high dose delay return time and cause fall in traction test. The observed effect demonstrates linearity with increasing dosage.
		Fireplace test	The jump time required by mice significantly increases in test group compared to the control group.
	Methanol and aqueous extract, with dose of 10, 30, and 100 mg/kg (Aris et al., 2013)	In vivo: locomotor test	The methanol extract demonstrates a dose-dependent reduction in animal locomotion, with the extent of reduction increasing with higher doses. Conversely, the aqueous extract also reduces locomotion, but variations in dosage do not yield significantly different results.
		In vivo: rotarod	There are no statistically differences between the methanol extract and the aqueous extract, as indicated by a p-value greater than 0.05. However, both extracts demonstrate observable effects when compared to the negative control.
Anxiolytic	Methanol and aqueous extract, with dose of 10, 30, and 100 mg/kg (Aris et al., 2013)	In vivo: elevated plus maze test	The methanol extract, administered at a dose of 30 mg/kg, and the aqueous extract at all doses exhibit an increase in the percentage of entries into the open arm compared to the placebo group.
Antidepressant	Alkaloid extract equivalent to 0.5 and 1 mg/kg of mitragynine (Buckhalter et al., 2021)	In vivo: Forced swim test	Low dose reduced immobility time, while high dose does not affect immobility time
Gastrointestinal	Methanol extract dose 50 – 400 mg/kg (Chittrakarn et al., 2008)	In vivo: castor oil-induced diarrhea	Methanol extract at dose 100, 200, and 400 mg/kgBW reduce defecation frequency and fecal weight. All doses can suppress intestine motility. The effect of extract 400 mg/kg is equivalent to loperamide 6 mg/kg.
Antioxidant	Ethanolic extract (Yuniarti et al., 2020)	DPPH	IC_{50} = 38.56 µg/mL

Activity	Materials and dose or concentration	Method	Result
	Aqueous, methanol, and alkaloid extract (Parthasarathy et al., 2009)	DPPH	IC_{50} methanol extract 37.08 ± 3.54 µg/mL IC_{50} aqueous extract 213.45 ± 31.31 µg/mL IC_{50} alkaloid extract 104.81 ± 5.77 µg/mL
Antimicrobial	Aqueous, methanol, and alkaloid extract (Parthasarathy et al., 2009)	Disc diffusion	The aqueous extract does not exhibit inhibitory activity. In contrast, both the methanol extract and the alkaloid extract demonstrate inhibitory effects against *Salmonella typhi* and *Bacillus subtilis*, with the methanol extract showing a minimum inhibitory concentration (MIC) of 6.25 mg/mL and the alkaloid extract with a MIC of 3.12 mg/mL.

Pharmacokinetics of Mitragynine

The pharmacokinetics of mitragynine, the primary constituent of kratom, has been extensively studied in both humans and animals (refer Table II). Following oral administration, mitragynine rapidly reaches peak concentration levels. The administration of kratom in capsule form or prior to food consumption has been demonstrated to impede the initial onset and prolong the time to reach peak effects. Mitragynine exhibits a double peak phenomenon, which can be attributed to various processes. One contributing factor is the impact of mitragynine on gastrointestinal function, leading to a reduction in intestinal motility and delayed gastric emptying. The inconsistent rates of gastric emptying and intestinal flow throughout the absorption process following a single oral dose of mitragynine could contribute to the erratic absorption of the compound (Avery et al., 2019). Additionally, due to mitragynine's low solubility in water, the insoluble fraction of mitragynine may be solubilized by bile salts and phospholipids released in the bile, potentially accounting for the second peak concentration (Maxwell et al., 2020).

Mitragynine possesses both hydrophobic and lipophilic properties, as reflected by its log P value of 1.76 (Ramanathan et al., 2015). It is considered as Biopharmaceutical Class System (BCS) Class II(Ya et al., 2019). As a poorly soluble drug, mitragynine exhibits low bioavailability, standing at only 17%, primarily due to its limited solubility. The residual of ingested mitragynine might undergoes processes such as first-pass metabolism, unchanged retention in the gastrointestinal tract, or degradation by the microbiota, a phenomenon commonly observed with herbal medicines.

Research conducted with a dose of 40 µg/mL indicates that mitragynine has high intestinal permeability in rats, with an in situ absorption model revealing a permeability coefficient of $1.11 \times 10{-}4$ cm/s. This value falls within the range of highly permeable drugs, suggesting that mitragynine readily crosses the intestinal barrier (Jagabalan et al., 2019). Due to its lipophilic characteristics, mitragynine exhibits extensive distribution throughout the body, with a volumetric distribution potential reaching up to 38 L/kgBW. The distribution pattern of mitragynine is hierarchically organized as follows: liver > kidney > lung > spleen > brain (Berthold et al., 2022).

Mitragynine is a P-glycoprotein (Pgp) with an inhibitory concentration (IC_{50}) of 18.2 ± 3.6 µM. Additionally, it inhibits CYP2D6 (IC_{50}, 0.45 ± 0.33 mM), CYP2C9 (IC_{50}, 9.70 ± 4.80 µM), and CYP3A4 (IC_{50}, 41.32 ± 6.74 µM). Consequently, caution is warranted during coadministration with other drugs that are substrates for this protein and enzymes. Monitoring is essential, as it may lead to an elevation in drug concentrations (Hanapi et al., 2013). In a documented case, a fatal interaction between mitragynine (MG) and the CYP3A4 substrate quetiapine occurred. The blood concentration of quetiapine in a 27-year-old individual, who tested qualitatively positive for mitragynine, was found to be fatal at 12 mg/mL. Importantly, there was no discernible disparity in pill quantities in the decedent that could reliably account for the postmortem blood concentration of 12 mg/L. It is suggested that the inhibition of CYP3A4 and/or P-glycoprotein (P-gp) by MG likely contributed to this fatal pharmacokinetic interaction (Hughes, 2019).

Considering the urinary excretion of the unaltered mitragynine form is as minimal as 0.14%, it is indicative of the extensive metabolism undergone by mitragynine. Mitragynine undergoes primary hepatic metabolism involving both phase I and II processes. One of its metabolites, 7-hydroxymitragynine, exhibits potent analgesic properties, surpassing the efficacy of morphine. Notably, 7-hydroxymitragynine exhibits efficient distribution to the brain and does not undergo reconversion to mitragynine (Berthold et al., 2022). While 7-hydroxymitragynine has a shorter residence time in the body, its presence as a metabolite of mitragynine leads to prolonged tissue retention, indicative of the governing role of its formation rate in elimination kinetics. In comparison to mitragynine, 7-hydroxymitragynine displays reduced tissue perfusion,

potentially attributed to dissimilarities in compound lipophilicity, resulting in a diminished capacity of 7-hydroxymitragynine, as compared to mitragynine, to traverse lipid bilayers (Berthold et al., 2022).

Table II. Pharmacokinetics Profile of Mitragynine

Pharmacokinetics in human (Trakulsrichai et al., 2015)	
T_{max}	0.83 ± 0.35 h
C_{max}	0.105 μg/mL
AUC_{0-t}	0.67 μg.h/mL
Vd/F	38.04 ± 24.32 (L/kg)
Cl/F	98.1 ± 51.34 (L/h kg)
$t_{1/2}$	23.24 ± 16.07 h
Protein binding	85 – 90% (Ya et al., 2019)
Pharmacokinetics in rat (Avery et al., 2019)	
T_{max}	1.5 ± 0.3 h, 3.8 ± 0.3 h
C_{max}	Peak 1 457.2 ± 42.3 and Peak 2 335.0 ± 34.3 ng/mL
AUC	2887.9 ± 177.9 ng.h/mL
Bioavailability	17.0%
Vd/F	33.8 ± 3.1 L/kg
Cl/F	7.1 ± 0.5 L/hr/kg
$t_{1/2}$	3.3 ± 0.2 h

Toxicity of Kratom

The side effects and toxic effect of kratom generally are similar to those of opioid, including weight loss, loss of appetite, dehydration, physical pain, constipation, fatigue, craving for opioid, decreased sexual performance, temporary erectile dysfunction, insomnia, depression, respiratory problem, hyperpigmentation, and psychosis (Saref et al., 2019). Other side effects of kratom are presented in Table III (Berthold et al., 2022; Hartley et al., 2022; Leong Bin Abdullah & Singh, 2021). As of December 31, 2020, the Food and Drug Administration's Adverse Events Reporting System public dashboard documented 567 fatal cases related to use of kratom alone or together with other substances. Of those, 378 deaths were officially reported (Berthold et al., 2022).

Specific cardiovascular effects of kratom were studied, revealing side effects such as tachycardia (21.4%), hypertension (10.1%), conduction defects (2.8%), chest pain (including non-cardiac pain; 2.6%), hypotension (1.8%), bradycardia (1.2%), and cardiac arrest (0.4%) **(Leong Bin Abdullah & Singh, 2021)**. Mitragynine, the active component in kratom, also affects the heart, potentially leading to prolonged QTc, which may cause torsades de pointes, a type of polymorphic ventricular tachycardia (Lu et al., 2014). Additionally, mitragynine has been associated with cardiorespiratory arrest and ventricular arrhythmia(Abdullah et al., 2019; Aggarwal et al., 2018).

Studies on the toxicity of kratom extracts show that the LD_{50} of methanolic extract is reported to be 90g/kg in mice (Vijeepallam et al., 2016). A 14-day evaluation of acute toxicity with standardized methanolic extract in rats revealed increased blood pressure one hour after administration, and the highest dose induced acute severe hepatotoxicity and mild nephrotoxicity. Sub-chronic high doses of methanolic extract for 28 days were found to damage the kidneys and lungs(Ilmie et al., 2015).

Compared to methanolic extract, alkaloid extract is reported to be more toxic. A recent study reported the death of rats after treatment with 200 mg/kg total alkaloid extract, with an LD50 value of 173.20 mg/kg in mice. Both kratom extract and mitragynine demonstrated cytotoxicity to human neuronal cells but showed no genotoxicity in the mouse lymphoma gene mutation assay.

In comparing the therapeutic index of alkaloid extract and mitragynine, mitragynine is found to be safer. The LD50 of alkaloid extract is reported to be 591.6 mg/kg, while mitragynine is 477.1 mg/kg. The ED50 of alkaloid extract and mitragynine were 194.4 mg/kg and 21.96 mg/kg, respectively, resulting in therapeutic indices of 3:1 and 21:1 for alkaloid extract and mitragynine, respectively. In comparison, the

therapeutic index of morphine is 70 (Sabetghadam et al., 2013). Hence kratom is not safer than standard opioid analgesic.

Table III. Side Effects and Toxic Effects Associated with Kratom Use

Organ Systems	Side Effects
Central Nervous System	Seizure
	Anxiety
	Posterior reversible encephalopathy syndrome
	Psychosis
	Coma
	Neonatal withdrawal syndrome
	Brain injury
	Insomnia
	Long-term cognitive impairment
	Confusion
Cardiovascular	QT prolongation
	Cardiac arrest
	Hypertension
Endocrine	Hypothyroidism
	Hyperprolactinemia
	Hypogonadism
	Anorexia
Gastrointestinal	Hepatic cholestasis
	Hepatitis
	Hepatomegaly
Respiratory	Respiratory arrest
Genitourinary system	Acute kidney injury
	Temporary erectile dysfunction
Skin	Hyperpigmentation
	Sweating
General	Lethargy

Conclusion

Kratom does indeed offer several health benefits, particularly as an analgesic. The diverse alkaloid composition and multifaceted mechanisms of action contribute to its potency, surpassing even that of morphine. However, the use of kratom poses numerous potential fatal risks, including respiratory failure, hepatotoxicity, cardiac arrest, physical and psychological dependence, and, in extreme cases, death. Despite its potent analgesic effects, it is argued that kratom is not inherently safer than morphine, as evidenced by a lower therapeutic index of its alkaloid extract and its isolate, Mitragynine.

Moreover, the consistency and predictability of kratom's efficacy cannot be assured, given its dependence on alkaloid content, influenced by various variables. Rather than advocating for the legalization of kratom as an herbal medicine, the author suggests that the cultivation or usage of the kratom plant should be restricted or banned due to the higher associated risks compared to benefits. Nevertheless, research into the potency of pure isolates from kratom, such as mitragynine or its metabolite 7-hydroxymitragynine, should continue, as these alkaloids hold potential as candidates for future medicines.

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