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REVIEW

Controversial usages of kratom (*Mitragyna speciosa*): For good or for evil

Murtadha Basheer, Rana Khudhair Jasim, Gam Lay Harn

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Abstract

Kratom (*Mitragyna speciosa*) is a plant that grows well in tropical climates such as in Southeast Asia. Traditionally, people discovered it possessed a stimulating effect that relieved tiredness. Furthermore, it contains analgesic and medicinal properties for the treatment of pain, diarrhea, muscle discomfort, and blood pressure and to enhance stamina. Nevertheless, long term or regular consumption of kratom leads to addiction. This is because the main alkaloid of kratom, mitragynine, binds to opioid receptors and exerts a euphoric effect similar to that of morphine, which may lead to death. Due to this reason, kratom has been listed as a regulated substance in many countries including the United States, Thailand, Malaysia, Bhutan, Finland, Lithuania, Denmark, Poland, Sweden, Australia, and Myanmar. Usages of kratom carry two pharmacological effects depending on dosage. Low-dose kratom exerts a stimulating effect that refreshes the user. High-dose kratom exerts sedative effects that can lead to addiction similar to that of morphine. Despite the euphoric effect of kratom, the beneficial values of kratom to human health is indisputable. Therefore, a complete banning of kratom may cause a loss to pharmaceutical industry. Rather, a controlled or selective usage of kratom will be a better choice.

Key Words: Kratom; Opioid; Pharmacological actions; Toxicity; Addiction; Herbal plant

Core Tip: Traditionally, people discovered kratom (*Mitragyna speciosa*) possessed a stimulating effect that relieved tiredness. Long term or regular consumption of kratom leads to addiction because the main alkaloid of kratom binds to opioid receptors and exerts a euphoric effect. Due to this reason, kratom has been listed as a regulated substance in many countries. Despite the euphoric effect of kratom, the beneficial values of kratom to human health is indisputable. Therefore, a complete banning of kratom may cause a loss to pharmaceutical industry. Rather, a controlled or selective usage of kratom will be a better choice.

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INTRODUCTION

Kratom (*Mitragyna speciosa*) (Figure 1) is a plant native to Southeast Asia. It has been planted as a recreational herb due to its analgesic properties[1]. Kratom was originally recorded for its stimulating effect. The leaves of the tree that are exploited for its pharmacological actions contain different colored veins (white, green, or red) that have been connected to a variety of effects[2]. The red vein leaf is popular in Thailand for its potency[3]. Traditionally, the raw leaves were chewed for their analgesic and soothing effect[2]. In addition, kratom leaves have been used to treat diarrhea, muscle discomfort, decrease blood pressure, and enhance stamina in Southeast Asia[4]. Antispasmodic, muscle relaxant, and antidiarrheal properties of kratom are still in use in the region, while its stimulant and analgesic effects are popular home remedies[3,5].

Folk medicine in Southeast Asia has recognized kratom as an herb[6] in the form of "herbal tea." Its use in the searing heat of the tropics helps workers stay alert and productive. Kratom is widely used to wean morphine addicts off the drug[7]. In fact kratom was utilized historically as an opioid substitute, and it was once widely used in Malaysia and Thailand as an opium replacement and countermeasure [8].

Nevertheless, kratom use has been banned by the local government in Malaysia[8], where it was classified as a poison under the Poison Act[6]. In Thailand, kratom was classified as a Schedule 5 substance under the Thai Narcotics Act. Bhutan, Finland, Lithuania, Denmark, Poland, Sweden, Australia, and Myanmar have kratom under control or regulation[6]. The United States also regulated the use of kratom when the United States Drug Enforcement Administration classified it as a drug of concern[9]. The Centers for Disease Control and Prevention (CDC) released a study on the harmful effects of kratom use on health, where 660 reports on the exposures were documented[10]. In addition, the CDC also documented hundreds of deaths connected with kratom usage[11,12]. Furthermore, the Food and Drug Administration does not acknowledge it as a recognized supplement. Subsequently, the prominence of kratom in the American psyche was reintroduced, where mitragynine and 7-hdroxymitragynine were announced as substances to be added to Schedule I of the Controlled Substances Act by the Drug Enforcement Administration. The Drug Enforcement Administration statement classified the chemicals as Schedule I, meaning kratom has no recognized medicinal value and a significant potential for misuse[13]. Despite all these regulations, several nations continue to allow kratom use today as there is no conclusive evidence that kratom use has the same negative health consequences as conventional opioids[14].

Although the Poisons Act of 1952 makes it illegal to consume kratom in Malaysia, the native tree and tea decoctions are abundantly available in the country[15]. In the United States, kratom products can be purchased from shops and online distributors. Kratom products are available in a variety of forms, including tablets, tea drinks, and powders[10,15]. Increased sales of kratom in Europe and North America have increased worries about its safety and prompted some European governments to prohibit the plant and its active alkaloids[16].

Kratom was legalized in Thailand in 2018 for therapeutic use after a prohibition on its usage, manufacture, and possession was overturned[17]. Following this legalization, many other countries may follow suit. In view of the potential negative effects of kratom, would this legalization be beneficial to society?

PHARMACOLOGICAL ACTIVE ALKALOIDS OF KRATOM

More than 40 compounds were isolated and chemically characterized from *Mitragyna speciosa* since the 1960s[18]. Thus far, only four of these components are pharmacologically active, namely mitragynine, 7-

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Figure 1 Kratom plant.

hydroxymitragynine, speciociliatine, and corynantheidine[19,20]. Mitragynine is the most common alkaloid of the kratom plant[21], and it can be easily oxidized[21]. Mitragynine makes up 66% of the alkaloid content of kratom. On the other hand, 7-hydroxymitragynine was identified as a minor ingredient of kratom leaves extract[6] that makes up 0.04% of the alkaloids[22]. Speciogynine, paynantheine, and mitraphylline are also indole alkaloids of kratom[23]. These compounds are not pharmacologically active, but they contribute synergistically to the overall effect of kratom that formed the diversity of alkaloids found in kratom extracts.

REPORTED MECHANISMS FOR PHARMACOLOGICAL EFFECTS OF KRATOM

Mitragynine and 7-hydroxymitragynine have the ability to target opioid receptors, yet their binding affinity to opioid receptors is significantly different[24]. Mitragynine has a lower binding affinity to opioid receptors than morphine, while 7-hydroxymitragynine is significantly more powerful than either, which is approximately 46 times the potency of mitragynine and 13 times the potency of morphine[25,26]. Therefore, 7-hydroxymitragynine has been targeted as the most important factor in the development of addiction and toxicity, while mitragynine poses a small danger[27,28]. The greater binding affinity of 7-hydroxymitragynine to opioid receptors is due to the addition of a hydroxyl group at the C7 position[19]. Both mitragynine and 7-hydroxymitragynine have been demonstrated to work as agonists, with mitragynine activating primarily μ- and δ-receptors and 7-hydroxymitragynine activating primarily μ- and κ-receptors[26,29,30]. Nonetheless, contradictory evidence suggests a different view. Rather than acting as simple agonists, mitragynine and 7-hydroxymitragynine appear to exert differential effects on distinct receptors[21] in which mitragynine and 7-hydroxymitragynine exert both agonistic and antagonistic characteristic upon binding to opioid receptors. On the other hand, they are partial agonists to μ-receptors, competitive antagonists to δ-receptors, and their effects on κ-receptors are very minimal[31].

Kratom contains indole alkaloids. These indole alkaloids are structurally and pharmacodynamically unlike its opioid rival. Therefore, they were identified as atypical opioids in order to distinguish them from morphine, semisynthetic opioids, and endogenous ligands[32]. Upon binding to opioid receptors, the indole alkaloids (such as kratom alkaloids) activate G-protein-coupled receptors. However, unlike conventional opioids (such as morphine), indole alkaloids do not initiate the β-arrestin pathway when they activate G-protein-coupled receptors[5]. This process refers to biased agonism or ligand-directed signaling that permits a single receptor to exert numerous distinct intracellular effects by selectively disabling the receptor's various signaling cascades[33]. It is worth noting that symptoms of opioid use like respiratory depression, sleepiness, and constipation are due to β-arrestin recruitment[34,35]. The selective β-arrestin inactivation by mitragynine is a desirable trait for an opioid. Therefore, mitragynine may serve as a useful template for the development of novel opioids with more tolerable side effects [21].

Apart from its opioid-like analgesic actions, mitragynine appears to inhibit pain signals *via* other pathways than morphine. Implying a multimodal involvement in pain perception regulation. For example, mitragynine bears a high degree of structural similarity to yohimbine, another indole alkaloid with well-documented adrenergic effects[24]. Due to this similarity, mitragynine analgesic properties

appear to act similarly as yohimbine, which is through activating the α-2 adrenergic postsynaptic receptors[36,37]. α-2 receptors are found in pain modulatory "descending" pathways. These pathways constitute a significant improvement in complicated neurobiological knowledge of pain[38,39]. Another study showed that mitragynine inhibits neuronal pain transmission *via* Ca^{2+} channel blockage[30]. When cellular connections are considered, the release of neurotransmitters was inhibited from the nerve terminals of the vas deferens[2] by the occlusion of neuronal Ca^{2+} channels[6,40].

The indirect analgesic qualities have been ascribed to anti-inflammatory activities of mitragynine, which are thought to be mediated through the suppression of *COX-2* and prostaglandin E2 mRNA expression[41,42]. Apart from these antinociceptive properties, mitragynine exhibits some affinity for D2 dopamine receptors, A2A adenosine receptors, and 5-HT2C and 5-HT7 serotonin receptors. All these belong to central nervous system receptors. Although the physiological significance of these interactions is unknown[30], postsynaptic α-2 adrenergic receptor stimulation and serotonergic 5-HT2A receptor blockage were reported to cause stimulant action of the central nervous system[43,44].

G-protein-biased signaling mechanism of action of mitragynine and 7-hydroxymitragynine makes kratom act as a partial agonist in terms of respiratory depressant effects[31,45,46]. The physiological impact of kratom is a combination of stimulant and sedative, depending on the dose. Stimulant effects are predominant at low dosages, while sedative effects are predominant at higher dosages[15,47]. This differential effect is due to the assortment of alkaloids shown in kratom extricates, which is a distinctive potential pharmacodynamic property of kratom[15,47]. At larger doses, kratom possesses unique narcotic qualities that blend psychostimulant and opiate-like effects[48]. Chronic usage of kratom has been linked to dependency[39].

PHARMACOLOGICAL EFFECTS OF KRATOM LEAVES

Consumption of 5-15 g of kratom leaves is believed to give opioid-like effects[24]. The euphoric effects begin around 10 min after consuming a few grams of dried leaves. At this dosage, kratom may give pain relief and alleviate symptoms of opioid withdrawal, with diarrhea as a possible side effect. Euphoria is more frequently attained at this higher level. Nevertheless, the effects are typically less powerful than with opioid medications[24]. Consumption of more than 15 g of kratom leaves could cause stupor, similar to the effects of opioids[24]. Most people will first suffer sweating, nausea, and dizziness. The early pleasure and tiredness are quickly replaced by a tranquil and dreamy state[44]. Tremors, anorexia, weight loss, convulsions, and psychosis have been reported in regular kratom users[6,24] who consumed high doses of kratom in a short period of time[6,24].

Synergistic effects of mitragynine and 7-hydroxymitragynine produce the analgesic effect desired by kratom users for self-treatment of pain and anxiety. Whilst these alkaloids exert sedative effects at high dosages (5-15 g), they exert stimulating effects at low levels (1-5 g)[44,47]. A dosage of 1-5 g of raw leaves is considered a low to moderate dose[16,24]. This dose is frequently associated with the stimulant effects frequently employed by laborers to combat weariness[24] and achieve greater work capacity while increasing attentiveness, sociability, and libido. Additionally, users may experience normal to slightly constricted pupils and blushing at this dosage. In general, adverse effects are mild. Nonetheless, anxiety and internal agitation have been reported[24]. Other effects of mitragynine included inhibition of ileum motility[7], smooth muscle contraction[49], and stomach acid production[50].

PHARMACOKINETICS AND DRUG-DRUG INTERACTIONS OF KRATOM

Kratom users should anticipate the full effects within 30-60 min after administration; however onset can occur as early as 10-20 min. Mitragynine and 7-hydroxymitragynine have half-lives of approximately 3.5 h and 2.5 h, respectively. Both are mostly removed from the body *via* urine[24,51]. The effects of kratom normally last between 5-7 h, with the biggest effects occurring between 2 and 4 h after administration. However, mild side effects can persist up to a day[24,43,52,53].

Kratom metabolism is primarily hepatic, and there is evidence that it can influence the metabolism and efficacy of other medicines by inducing drug-metabolizing enzymes, namely CYP450s and UDP-glucuronosyl transferase (UGT)[54]. The effects of kratom on human recombinant CYP450 enzyme activity have been studied in various research[55]. Herb-drug interactions were observed when mitragynine was used with herbal or modern medications that share the same metabolic pathway[56]. Mitragynine has a half-life of as little as 3 h, although it may be longer as suggested by others[57,58]. Significant advancement in kratom pharmacology conception revealed that mitragynine is transformed *in vivo via* hepatic metabolism into 7-hydroxymitragynine[59-61]. As a result, it has been hypothesized that 7-hydroxymitragynine is the active metabolite of mitragynine responsible for the majority, if not all, of the effects usually ascribed to the mitragynine precursor. Mitragynine is activated by CYP34A-mediated dehydrogenation, a mechanism akin to how opiates such as codeine are activated *via* CYP2D6-mediated dehydrogenation. In spite of the fact that 7-hydroxymitragynine is found in kratom extracts at minimal levels, the endogenous synthesis of 7-hydroxymitragynine from mitragynine was

significant[59,60,62].

In contrast to oral treatment, intravenous injection of mitragynine in rats was shown to be rapidly distributed to the peripheral compartments through systemic circulation or the central compartment[63, 64]. Mitragynine has a high intestinal permeability in rats. Mitragynine and 7-hydroxymitragynine can pass the blood-brain barrier and are dispersed throughout the brain. Mitragynine has a larger blood-brain barrier permeability and is more readily absorbed into brain tissue than 7-hydroxymitragynine[62, 65]. Mitragynine and 7-hydroxymitragynine inhibit P-glycoprotein[58,61]. These findings indicate that kratom not only penetrates the blood-brain barrier but also inhibits the brain from excreting other compounds *via* the P-glycoprotein efflux mechanism, hence enhancing the bioavailability of sensitive medicines.

Given the rise of reports on toxicity when used in combination with other drugs[66-70], it is worthwhile to investigate the pharmacological interactions of kratom. Drug-drug interactions by modulation of hepatic P450 activity and drug metabolism have been demonstrated in animal investigations[54,55]. Mitragynine appears to inhibit hepatic demethylases, transferases, and the glucuronidation reaction spurred by UGT like UGT2B7 and UGT1A1[71-74]. This has a major indication for the possibility of interaction of kratom and other UGT substrates, such as buprenorphine and ketamine, which are metabolized by UGT2B7[74]. These findings have been cited as a possible explanation for cases of toxicity associated with co-administration of kratom and other drugs, including a fatality associated with supratherapeutic doses of a prescription antipsychotic concomitant with kratom ingestion[67].

A proposed explanation for drug-drug interactions is the effect of kratom on the cytochrome P450 system, a set of enzymes involved in the metabolism of a wide variety of drugs[75]. Two of the most important enzymes involved in drug metabolism are CYP2D6 and CYP3A4. Mitragynine inhibits CYP2C9 and CYP2D6 in a noncompetitive manner and CYP3A4 competitively[56] indicating that kratom has tremendous interaction potential[75]. The largest inhibitory impact is observed for CYP2D6 and CYP3A4, indicating compounds that share the same metabolic route may contribute to unfavorable interactions[55,56]. Due to the inhibitory effects of kratom, substrates for these enzymes may accumulate, leading a typically safe dosage to reach hazardous levels. Thus, while one of kratom's active ingredients, 7-hydroxymitragynine, is mostly responsible for the herb's sedative and analgesic properties, the other active ingredient, mitragynine, may be the cause of unfavorable medication interactions *via* its influence on cytochrome P450 enzymes. It is obvious that identifying herbs as possible medication inhibitors may assist or limit the risk of adverse effects associated with herb–drug interactions[55].

BENEFIT AND RISK OF KRATOM USAGE

Concerns regarding the potential of kratom dependency and addiction in humans are well founded[30, 76,77]. However, for many frequent users, the primary objective was merely to avoid weariness and to boost energy. In such instances, frequent usage may not be defined as dependency or addiction but rather as a desire to increase productivity[78]. This is consistent with "drug instrumentation" hypotheses, according to which a substance is used for a specific, planned aim[6,79]. Long-term use of kratom may result in adaptation, where outright addiction was reported under certain circumstances [76]. It has been suggested that a considerable percentage of kratom usage happens as a substitution for more hazardous drugs, particularly opioids in individuals who already have a history of substance misuse. In these circumstances kratom use is considered harm reduction rather than drug abuse[6,80].

Apart from its misuse potential, kratom poses a slew of additional dangers to patients, mostly as a result of its status as an unregulated supplement. Nothing can be done to assure the veridicality, pureness, grade, and safety of commercially accessible kratom formulations in the absence of governmental control[81]. As a result, it is impossible to determine exactly what is contained in commercially available kratom formulations. Furthermore, the quantity of mitragynine can vary significantly[22]. There have been reports that kratom products can be enhanced in potency by intentionally raising the quantity of 7-hydroxymitragynine[82]. Additionally, many cases of purposeful adulteration of kratom have been observed, including the insertion of synthetic drugs such as phenylethylamine or O-desmethyltramadol, both resulting in patient fatalities[83,84]. Additional dangers include purposeful or accidental product contamination. Laboratory and epidemiological evidence in 2018 specified that kratom was the cause of salmonella infestation[85]. In addition, there have been instances of kratom products being sold that were later shown to have dangerous heavy metal impurities[12].

ADVERSE EFFECTS OF KRATOM USAGE

Kratom side effects, particularly for regular heavy kratom users, were agitation (18.6%), followed by tachycardia (16.9%), sleepiness (13.6%), and disorientation (8.1%)[86]. Seizures occurred in 6.1% of patients, hallucinations in 4.8%, and coma in 2.3%. Other symptoms include weight loss, frequent

urination, insomnia, fatigue, constipation, dry mouth, nausea, and hyperpigmentation of the cheeks[43,44]. Withdrawal symptoms due to the sole usage of kratom are too mild to be detected even for heavy users[44]. Apart from the initial adverse effects of kratom consumption, persistent and high-dose use results in various major side effects such as respiratory depression[66]. Injury to the liver, heart, lungs, kidneys, and neurological system are more significant and life-threatening adverse effects[87].

Concurrent use of kratom and other drugs has been associated with the development of focal and generalized tonic-clonic seizures, possibly as a result of the inhibitory effect of the active components of kratom on cytochrome P450 enzymes and P-glycoprotein[88]. Death was reported in 91 (59.9%) of 152 kratom-positive persons as documented by the unintentional drug overdose reporting system of the United States[89]. Co-administration of kratom and other medicines has the potential to enhance toxicity. A combination of mitragynine and morphine has been found to improve analgesia and delay the development of morphine tolerance in rats[90]. It has been reported that kratom extracts may alleviate symptoms of ethanol withdrawal by lowering alcohol consumption[91].

Muscle relaxation is a common physiological consequence of opiate usage and is frequently noted in kratom users[92]. Mitragynine and other kratom alkaloids may operate similarly to other opiates on the neuromuscular junction[92]. Mitragynine may also cause mild tremors and stiff fingers and toes[93]. This might be explained by the way stimulant and depressive effects are classified at low and high dosages, respectively. Seizures have been observed following kratom usage[92]. Intriguingly, seizures associated with kratom usage doubled in Thailand between 2005 and 2011[16].

A more recent study revealed that kratom caused hepatotoxicity in patients[94]. In addition, kratom-mediated liver damage, stomach pain, jaundice, pruritus, and dark urine were often reported as presenting signs and symptoms[95]. Autopsy results of kratom-related fatalities showed the presence of edema in the brain and lungs, as well as congestion in several organs[96].

A variety of organ systems can be affected due to kratom usage, which include kidney injury[97], cardiotoxicity and arrhythmia[98,99], thyroid injury and hypothyroidism[100], lung injury/acute respiratory distress syndrome[101,102], neonatal abstinence syndrome[103-107], and hepatic injury[108-111]. Amongst these, hepatic injury such as cholestatic hepatitis pattern similar to other drug-related injuries is frequently reported[112]. A number of neurological problems associated with kratom toxicity, including acute brain damage and coma, were documented[112].

Toxicity of kratom is dose-dependent, especially when kratom powder dosages surpass 8 g[86]. An overdose fatality from kratom alone is not common, although it has been reported in the United States and Southeast Asia[113]. This is in line with pharmacologic research and epidemiological investigations of kratom in Southeast Asia. Unlike morphine-like opioids, kratom does not cause life-threatening respiratory depression and is not linked to the personal and societal impairment that morphine-like opioids are linked to[3,8,113].

CONCLUSION

Kratom exerts its pharmacological effects in a dose-dependent manner, where it acts as a stimulant at low doses and a depressant at high doses. Regular usage of kratom can lead to dependency. The cellular mechanisms of kratom are complex and not well understood. The major alkaloid of the kratom leaves, mitragynine, and its minor alkaloid, 7-hydroxymitragynine, are likely responsible for the pharmacological effects of kratom. As the data have shown so far, deaths due to the sole use of kratom are rare. Typically, the combination use of kratom with other illicit drugs are the main causes of death. Given the valuable therapeutic properties of kratom, total banning of kratom will be a great loss to the pharmaceutical industry. Instead controlled usage should be practiced especially in the event of kratom misuse for recreational purposes. Considering both benefits and risks of kratom usage, one can wisely choose to use it for good.

FOOTNOTES

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