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Review

Healthcare Provider's Guide to Kratom: Succinct Introduction to the Basics and the Questions

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Abstract

***Background*:** The leaves of *Mitragyna speciosa* (kratom), a tropical tree that is indigenous to Southeast Asia, have been used traditionally to increase stamina, as a digestive aid, and as an analgesic. Kratom use is now increasingly popular in the rest of the world because of easy availability through the Internet and real, or perceived, views of efficacy and safety**.**

***Methods*:** PubMed and MedLine searches were conducted of published articles available in English.

***Results*:** Mitragynine and 7-hydroxymitragynine are the primary psychoactive compounds of the over 25 alkaloids in kratom. Subjective effects are dose dependent: a mild stimulation at lower doses, sedative effects at intermediate doses, and mild opioid-like effects at higher doses. Toxicity is rare and may be due instead to polypharmacy. Abrupt discontinuation after extensive use can produce withdrawal symptoms, but use does not imply overt dysfunction or decreased quality of life. In fact, Kratom has been used by opioid substance abusers as a

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means of easing withdrawal. Indeed, the use of kratom as a safer choice than opioids is an argument against overzealous regulatory control. Potential therapeutic utility as a mixed-acting analgesic agent, anti-inflammatory, and possibly anticancer agent are currently being investigated.

***Conclusions*:** Kratom or one or more of its constituent substances likely have important therapeutic potential – or as drug-discovery leads – as analgesics, treatment or prevention of opioid use disorder, and possibly other medical conditions. Since its use as a recreational drug is also on the rise, it is imperative that healthcare providers and regulators maintain an open mind and support the need for more basic and clinical research to help elucidate the actual potential medical benefits and potential adverse effects of this simultaneously old, yet new, pharmacologic agent.

Keywords

Kratom; pharmacology; therapy; opioid-abuse treatment

1. Introduction

Mitragyna speciosa (kratom) is a tropical tree of the Rubiaceae family (of which coffee is also a member) that is indigenous to Southeast Asia. Leaves from the tree (see Figure 1) are traditionally used (chewed) by laborers to increase energy and stamina [1], or for medicinal purposes such as pain relief, digestive disorders, and even to attenuate morphine withdrawal [2].

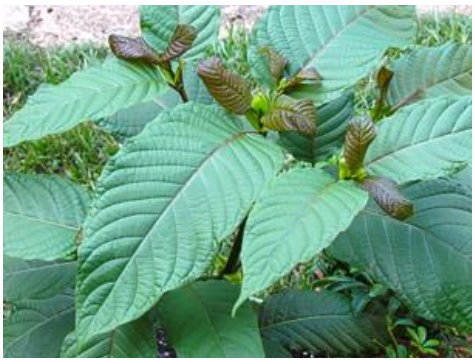

Figure 1 Kratom plant (photo credit: Wikimedia Commons).

Kratom has become increasingly popular and visible in the rest of the world in recent years [3]. As a natural substance with a long history, this ethnodrug known variously as 'kratom', 'ketum', 'biak' (Malaysia), or 'krathom' (Thailand) among others, is both scientifically interesting and a potential concern to healthcare providers and regulatory agencies because not enough is understood about its pharmacologic or adverse effects. Complicating things, as an unregulated natural product, the exact composition of a given commercial product is often unknown.

2. Materials and Methods

Online sources such as PubMed, MedLine, and news media were searched for publications and articles available in English with titles or search terms relevant to the topic. Search terms included kratom (and regional synonyms such as biak, *etc*.), *mitragyna*, mitragynine, 7-hydroxymitragynine, plus terms related to specific pharmacology (*e.g*., mu- delta- and kappa-opioid receptors, affinity, efficacy, biased ligand, *etc*.). References within each citation were also searched. To the best of our ability the pertinent information, or at least the essence of the information, has been distilled herein from the several hundred 'hits'.

3. Results

3.1 From Traditional to Contemporary Use

Kratom has been used for centuries by manual laborers in Southeast Asia countries to enhance mental-alertness and increase stamina. In some communities, kratom leaves have also been part of traditional folk medicine, and as such it has been used to treat a variety of medical conditions, including diabetes, fever, and diarrhea. Its efficacy for pain-relief (analgesic agent) is well known to traditional practitioners [4]. It is sometimes also used as part of religious ceremonies and at social and community gatherings [5]. Until recently, Malaysia and Thailand were the main geographical areas of kratom use. Surveys reported lifetime prevalence of use of about 2% [6] to 5% [7].

However, although kratom is legal in parts of the world, including much of the United States, it is not devoid of potential problems. For example, kratom is the most frequently used illegal drug in Thailand [8]. It is also illegal in Malaysia, but it may be more openly available from suppliers and coffee shops [9]. Thailand very recently approved the use of kratom plants for medicinal use. In the West, kratom can be obtained from online sources and from specialty shops and bars [10]. Some Internet sources of kratom market it as a supplement or herbal product, which may lead certain purchasers into thinking that the product is completely harmless because it is a "natural" substance [10, 11]. The legal status of the drug in the United States allows people to use the drug without exposure to legal risks. It has even been promoted as a "safe, legal high." [3, 11].

Multiple sources provide kratom powder made from dried leaves [12]. Consumption patterns can vary by location (with much overlap): chewing kratom is common in Thailand, drinking kratom-infused beverages is more common in Malaysia, and powders and capsules are more popular in the West [13]. Historically, kratom leaves (fresh or dried) have been brewed into a tea, smoked or chewed [14], which is how manual laborers in rural Southeast Asia came to be known as "kratom eaters" for the habit of chewing fresh leaves throughout the day [1]. The leaves have a bitter and unpleasant taste, so some users prefer to make it more palatable by infusing it into tea, coffee, or other beverages and adding milk, sugar, or other flavorings. Recently, "4 x 100" cocktails are being used by young people in countries that prohibit alcohol (the name from the four main ingredients of a sweet caffeine-containing beverage, kratom, codeine, and variably some antidepressant or anxiolytic drug, served over ice, yielding a drink that reportedly mimics the effects of liquor) [6, 15].

Although Malaysia strictly regulates kratom and penalizes possession [3], rural communities do not look down on its use by laborers, provided that the use is for work to support their families [1]. There is little discrimination or disrespect for kratom users, although some family members may

rebuke regular users for spending too much money on their 'habit' [2]. In fact, Southeast Asia kratom users may be viewed by their peers as particularly diligent people, taking advantage of the drug's energizing effects in order to work longer hours and earn more money for their families [1]. And in contrast to individuals who use other substances, habitual kratom users in Southeast Asia tend to be older, married, and living together with the families that they support [1, 7, 9].

In the West, kratom has historically been viewed as something of a novelty, a natural herbal product with possible therapeutic benefits, or even as a legal high. Many in the West still view kratom as mild and completely harmless, partly because it is considered a natural substance and partly because there are few laws restricting its use.

It is not known if long-term excessive use of kratom leads to social, physical, or psychological problems [3]. Kratom use can lead to the development of physical dependence and withdrawal symptoms upon too abrupt discontinuation [16]. However, the assumption by some that these are definitive signs of 'addiction' is outdated and inaccurate, since they are physical phenomena that result from basic pharmacologic principles and apply to almost all drugs.

3.2 Kratom and the Law

The laws regarding kratom can be convoluted, complex, or altogether confusing. For example, kratom has been technically outlawed in Thailand since 1943 [3], where it is illegal to plant, grow, possess, import, or export kratom leaves [7]. Nevertheless, kratom is widely used in Thailand and users do not experience particular social stigma. Now, Thailand has very recently approved the use of kratom plants for medicinal use. Kratom is a controlled substance in Australia, Bhutan, Malaysia, Myanmar, and other countries [17], but it is legal to cultivate kratom in Malaysia as long as it is not consumed, distributed, or prepared for distribution (leaving one to wonder what else is there) [9].

Only a few European nations have regulations specifically addressing kratom [18], and kratom is largely uncontrolled in the United States (but there is currently a very intense debate on this subject) [13]. This may also make it particularly appealing to risk-averse recreational users [19]. While the United States and United Kingdom do not regulate kratom, the United States Food and Drug Administration (FDA) has issued an import-alert warning about possible side effects [20]. And the United States Drug Enforcement Administration (DEA) has added kratom to its list of "Drugs and Chemicals of Concern." [21, 22]. The FDA has seized certain products containing kratom, but typically only in products where kratom is used in dietary supplements. The import-alert of 2014 allows officials to interdict such products when the agency believes that the product is adulterated [20]; the United States Department of Justice has ruled that kratom is a dietary ingredient for which there is not sufficient reasonable assurance that it does not present risk of illness or injury. Large seizures of imported dietary supplements containing kratom have occurred [23, 24]**.**

3.3 Pharmacologically Active Compounds in Kratom

The main active compounds in kratom leaves are the alkaloids mitragynine and 7-hydroxymitragynine, plus speciogynine, paynantheine, and speciociliatine [6]. It contains dozens of different but structurally related alkaloids along with flavonoids, terpenoid saponins, polyphenols, and glycosides [3].

The alkaloid content of kratom is about 0.5% to 1.5% [25, 26], which varies from plant to plant, and depends upon the strain, its location of cultivation and the season [27]. Mitragynine is

lipophilic, with poor solubility in water [28]. The alkaloid fraction of mitragynine can be as high as 66% for kratom from Thailand or as low as 12% for kratom from Malaysia [29]. Although structurally dissimilar to morphine and other opioids, mitragynine has some affinity for opioid receptors [30]. All of the mitragynine analogs in kratom (*e.g*., speciogynine, paynantheine, and speciociliatine) are indole alkaloids with a monoterpene moiety [29]. 7-Hydroxymitragynine is more potent than mitragynine in *in vitro* and *in vivo* tests [29, 31, 32].

Botanically, there are three main strains of kratom. The red variety originated in Bali and is known in folk medicine as an effective pain reliever. The green and white varieties originated in Malaysia and have a reputation for their stimulating effects [33]. Buyers who shop online may find "brand names" such as Bali kratom, Malaysian kratom, Thai kratom, Maeng Da kratom, white-veined Borneo kratom, Java kratom, Sumatra red, and so on [27]. Online sellers have attempted to rank kratom by grade in terms of potency with "organic commercial grade" the least and "super" or "super enhanced" the most potent forms [33]. However, these grades are marketing terms used by those selling kratom and have not been subjected to any form of scientific scrutiny or objective analysis.

3.4 Pharmacology

The exact pharmacological mechanism(s) responsible for producing kratom's characteristic effects have yet to be established [34-37], Some of the earliest work on the basic science of kratom was done by Macko *et al*. [38], who reported among other things the antinociceptive effects of mitragynine in mice (hot-plate test), rats (tail-flick and paw-pressure tests), and dogs (hindleg flick). The pharmacologic response to kratom [3] varies among individuals, which might result from kratom's hydrophobicity, poor solubility in water, variable drug release in body fluids, and variable acid degradation properties. Kratom's subjective effects depend on dose: stimulation is characteristic of low doses, analgesia and sedative effects of higher doses [39]. Interesting recent studies suggest that the differences from traditional poppy-derived opioids might be attributable to the G protein 'biased signaling' nature of interaction at the mu-opioid receptor [40, 41].

Kratom is mainly metabolized in the liver [42, 43]. In a study on human recombinant cytochrome P450 (CYP450) enzymes, mitragynine produced a strong inhibitory effect on CYP3A4 and CYP2D6, moderate inhibition of CYP1A2, and weak inhibition of CYP2C19. This suggests that concomitant use of kratom and other drugs that act as substrates of these enzymes might result in potential drug interactions [6, 25, 44]. In a pharmacokinetic study of healthy subjects who regularly used kratom, mitragynine levels declined exponentially, suggesting a two-compartment model [45]. About 0.14% of mitragynine was excreted unchanged in the urine [45].

3.5 Adverse Effects and Toxicity

Oral doses of total alkaloid extract of *Matrigyna speciosa* at 200 mg/kg were lethal to rats [46]. The lethal dose 50% (LD50) for mice was 477 mg/kg for mitragynine and 591 mg/kg for alkaloid extract [39]. The therapeutic index for the alkaloid extract compared to mitragynine was 3:1 and 20:1, respectively [28].

The literature contains a few reports of putative kratom-related fatalities, but most involve poly-substance use, so it is difficult to attribute causality [47]. Preclinical reports or individual case

reports of excess kratom use have suggested adverse effects, but more well-validated clinical research is clearly needed [17, 48-53].

Those who used kratom regularly over extended periods of time have reported weight loss, dehydration, constipation, hyperpigmentation, lethargy, and fatigue [9]. Other adverse effects, including trembling hands and headaches, have also been reported [7].

3.6 Abuse Potential

Kratom appears to have some potential for abuse [1, 7, 8]. And abrupt discontinuation of regular kratom use can produce mild withdrawal symptoms (*e.g*., irritability, lethargy, yawning, rhinitis, muscular aches and pains, cramps, and diarrhea) [1, 8]. 'Psychological' withdrawal symptoms are reported also (tension, restlessness, aggression, sadness, delusions, hallucinations, moodiness, anxiety, and cravings) [8, 16]. Other reports add insomnia and pruritus [54]. The withdrawal symptoms may persist for a few days [16], but compared to withdrawal from other substances, the kratom experience has been described as generally shorter and not as distressing [16]. Regular kratom users in Malaysia did not exhibit social dysfunction compared to non-users, and none were involved in criminal activities to support their habit [55].

Concern of potential abuse is expressed because low doses act as a stimulant and therefore might pose the risk of a milder version of the stimulation produced by amphetamines or cocaine, and higher doses produce more sedative effects, possibly posing the risk of a milder version of opioids [56-58]. In some preclinical studies, mitragynine has been reported to be mildly rewarding, or to impair learning and memory [51, 59, 60]. But recent studies have shown that mitragynine is not self-administered by rats [61, 62].

Dose-dependent stimulatory and sedative effects of kratom, potentially attractive to some users, suggests that a small subset will abuse it, as occurs in locations where the plant grows indigenously [1]. Ready Internet access, and low price also suggest that it will become increasingly popular among recreational users [9]. On the other hand, the use of kratom instead of dangerous drugs of abuse would represent a net plus to individuals and society. Hence the on-going regulatory debate.

Kratom constituents are not currently detectable in conventional urine drug screening assays, but chromatography-tandem or ion-mass spectrometry instruments can detect kratom [3, 10, 13]. Kratom was added to the Monitoring List of the World Anti-Doping Agency in sports in 2014. There are currently no standardized screens for mitragynine other than liquid chromatography-mass spectrometry [25].

3.7 Clinical Response to Kratom Toxicity

Kratom toxicity has been reported, but mainly in the form of case reports – and almost always involving polysubstance use – making it difficult to draw conclusions. The symptoms of kratom toxicity have been reported to include heart palpitations, seizures, and coma [63, 64]. One case of intrahepatic cholestasis has been described in a young male who used kratom for two weeks [49]. The literature reports fatalities associated with the use of kratom, but polydrug use is almost always involved [41, 44, 63, 65]. The relative toxicity of mitragynine and 7-hydroxymitragynine remains to be elucidated. Reports almost never include the relative concentrations, which may or may not be an important consideration [66].

Patients with kratom overdose should be considered for detoxification, which should be undertaken in clinic. The clinical team should ascertain what the patient took and if multiple substances might be involved – which is highly likely. Patients undergoing withdrawal should receive supportive care and should be treated in accordance with detoxification protocols.

3.8 Clinical Response to Kratom Dependence/Abuse

The literature reports a case of "addiction" and detoxification in a 37-yr Caucasian woman who was introduced to kratom by a colleague for pain control. She soon began buying kratom online because in addition to analgesic benefits, it gave her the added energy that helped her manage her busy schedule [67]. She presented in kratom withdrawal and was initiated on an opioid withdrawal protocol in the hospital using symptom-triggered clonidine at a dose of from 0.1 to 0.2 mg/kg every two hours based on her Clinical Opioid Withdrawal Scale (COWS) score; she also was administered 50 mg oral hydroxyzine every six hours and 0.1 mg/day clonidine *via* a transdermal patch. She experienced severe withdrawal symptoms on the COWS scale which improved rapidly by the third day. Following detoxification, she experienced symptoms of depression and was discharged from hospital with counseling and oral naltrexone 50 mg [67]. There is no current consensus as to the best way to manage kratom withdrawal. It has been suggested that combination therapy including alpha-2 agonists and hydroxyzine may be efficacious in relieving the physical and mental symptoms [67]. Once the patient has successfully discontinued kratom, maintenance strategies are also unclear. While it has been suggested that buprenorphine or methadone be used as maintenance therapy, kratom is not of the opioid class and this raises regulatory issues regarding the appropriateness of using opioids for kratom maintenance [67]. Naltrexone (an opioid antagonist) may be helpful in that it may attenuate cravings, as it does for alcohol [67].

4. Discussion

As kratom use increases in the United States, people will seek advice from clinicians about it, because they have used it, want to try it, or because they are concerned about another person using it. Some patients may believe or assume that it is a safe herbal supplement or some kind of natural pain reliever. Others think it should be outlawed entirely. Clinicians should know the legal status of kratom in their state and municipality and remind patients that although it is a natural (and often legal) substance, it can still have as yet unknown potential adverse effects.

4.1 Kratom's Potential Role for the Treatment of Opioid Withdrawal

Kratom is sometimes used as a safer, legal alternative to other substances [9, 13]. It has also been used to help relieve opioid withdrawal symptoms and as an aid for those seeking to discontinue opioid use [9]. Migration from opioid use to kratom use has been documented in Southeast Asia [5]. Clinical trials of the value of kratom for treatment of opioid abuse and of alleviating withdrawal symptoms is a topic worthy of further study.

4.2 Therapeutic Potential of Kratom

The components of kratom have been studied in a variety of preclinical *in vitro* and *in vi*vo tests [10, 25, 56, 68, 69]. Methanolic and alkaloid extracts significantly prolonged response latency in the hot-plate test, indicative of analgesic activity [70, 71]. Mitragynine had antinociceptive properties when administered either orally or intraperitoneally to rats [72]. Oral or subcutaneous mitragynine produced potent antinociceptive effect in the tail-flick and hot-plate tests in mice [73].

Kratom is sometimes marketed—openly—as an herbal supplement for pain control [53, 74, 75]. The analgesic properties of kratom and those of its major active principal mitragynine are subjects worthy of study in clinical trials.

Mitragynine may also exert an anti-inflammatory effect [29, 30] by suppressing prostaglandin E2 (PGE-2) in the cyclooxygenase (COX) 2 pathway [32]. It has also been suggested that mitragynine may possess anticancer properties [76]. Kratom extracts and mitragynine have displayed cytotoxicity to certain human cancer cell lines (*e.g*., SH-SY5Y) [77]. Mitragynine may modulate muscle neurogenic contraction [78-80], and gastric secretion [81], consistent with traditional use. There are also anecdotal reports that it has aphrodisiac properties [9].

5. Conclusions

Kratom, long used in Southeast Asia as a work-enhancing energizer and traditional remedy, is rapidly growing in use in the West as a result of availability through the Internet, aided in part by its current non-scheduled status and perception by some that it offers a safe all-natural high. In low doses users experience a pleasant stimulation, sedation and analgesia at moderate doses, and mild opioid-like effects at high doses. There are reports of withdrawal symptoms if the drug is abruptly discontinued after long-term use. Kratom components – or analogs of them – might have therapeutic potential for several conditions, including pain relief and opioid use disorder. Its use as a recreational drug is very likely to increase, raising a dilemma for healthcare providers and regulators: should it be tightly regulated, or should it be viewed as a better option than ‘hard’ drugs – and therefore controlled more like ethanol. It is important that clinicians familiarize themselves with this substance and how to counsel patients with respect to its use. It is also important that they be proactive in the debate and the decision process regarding scheduling kratom as a controlled substance. It is either the next drug of abuse or a panacea to the opioid crisis – or, most likely, something in between that requires mature, informed decision-making.

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Author Contributions

These authors contributed equally to this work

Competing Interests

The authors have declared that no competing interests exist.

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