Kratom Fact Sheet for Healthcare Professionals

1. Introduction

Kratom is both the whole tree *Mitragyna speciosa* in the family Rubiaceae as well as the leaves and extracts of the leaves that are used for medicinal and recreational purposes [1]. The tree is native to Southeast Asia and primarily grown in Malaysia, Thailand, and Indonesia. It is occasionally cultivated in other countries including the US. It is also known as ketum, biak-biak, Maeng Da, thang, thom, and kakuam, among others [2].

2. History of use outside and in the US

Traditional use of Kratom in Southeast Asia was first reported in 1836 but likely dates back further primarily for two reasons: as an opium substitute in Malaysia and as a stimulant to increase work efficiency in Thailand [3]. Kratom is used alone or brewed in combination with cough syrup (often codeine) and Coca Cola, then referred to as 4x100 as a drug of abuse, in Southeast Asia [4]. Its first use in the US remains unknown but cases emerged in the early 2000s describing Kratom for self-treatment of opioid withdrawal symptoms, pain, and mental conditions [5]. The CDC reported an increase in calls to Poison Control Centers involving Kratom and the FDA has warned consumers to avoid taking Kratom [6, 7]. As of February 2019, the FDA recommends placing Kratom's active compounds, mitragynine and 7-hydroxymitragynine, in DEA schedule 1 because of their opioid-like effects and potential for dependence without any current medical indication in the US.

3. Traditional uses

In Southeast Asia, fresh Kratom leaves were chewed to increase work efficiency and relieve fatigue for manual laborers. Fresh and dried leaves were also brewed into teas in Malaysia and Thailand for a range of ailments including diabetes, diarrhea, fever, pain, and for use as a wound poultice [8]. It was and remains used as a substitute for opium and to reduce opioid withdrawal symptoms both in Asian countries and in the West. There is no scientific information on traditional uses of Kratom preparations before the 2000s outside of Asia.

4. Dosage forms, dose range; differentiation between pure Kratom and adulterated products

Kratom is primarily consumed orally. It is available in the US as powder, tablets, capsules, raw leaves (mostly dried), and concentrated extracts (most containing varying amounts of ethanol). The doses range widely based on the dosage form with powders usually suggesting a dose of 3-5 g while concentrated liquid extracts may only require 1-2 drops to be added to a beverage according to manufacturer recommendations. Users may administer the extracts several times per day to achieve improvement of their condition although a majority appear to use the extract 3 times/day in doses of 3-5 g [9]. Self-dosing in combination with currently unregulated Kratom product quality results in highly variable concentrations of the active ingredients mitragynine and 7-hydroxymitragynine. Pure Kratom products should contain no more than 66% of mitragynine as the main alkaloid and 2% of 7-hydroxymitragynine in the alkaloid fraction of the extract or a total of approximately 2% of alkaloids (1.8-2% mitragynine and 0.02-0.03% 7-hydroxymitragynine) in the whole leaf extract [10, 11]. Kratom preparations are known to be adulterated in Western countries with various synthetic compounds including 7-hydroxymitragynine, O-desmethyltramadol (then referred to as "Krypton"), fentanyl, hydrocodone and other prescription opioids [10, 12].

5. Potential uses, what consumers and patients may use it for

Because of its many traditional uses as both a dose-dependent stimulant and analgesic, Kratom preparations may be used for a wide range of self-treatment options by patients. Surveys and case reports describe the use for acute and/or chronic pain, mitigation of opioid, prescription and other drug dependency withdrawal symptoms, substitution of opioid medication or illicit opioid drugs, harm reduction measures in opioid withdrawal, depressive or anxiety disorders, attention deficit and hyperactivity disorders (ADHD/ADD), bipolar disorder, post-traumatic stress disorder (PTSD), and other conditions [5, 9, 13]. In addition, a person may use Kratom recreationally to obtain relaxation, improved mood, increased energy, or an altered state of consciousness ("high") especially if used in combination with other drugs such as alcohol, benzodiazepines, opioids, cocaine, or amphetamines [13].

6. Current known pharmacology, active pharmacological principles

Early investigations of whole Kratom extracts indicated that the extract exerted a stimulant effect in both humans and animals "comparable to cocaine" but only a weak analgesic effect equivalent "in potency to that of codeine" [3]. Following isolation of the indole alkaloids mitragynine and 7-hydroxymitragynine from enriched extracts, both were found to be partial agonists at the μ-opioid receptor [11]. Mitragynine binds with much lower affinity to the receptor compared to morphine (EC_{50}=339 nM for mitragynine vs. EC_{50}=3 nM for morphine) while 7-hydroxymitragynine is about 10 times more potent than mitragynine at the receptor with an EC_{50}=35 nM *in vitro*. Other alkaloids from Kratom bind as competitive antagonists to the μ-opioid receptor thus resulting in a potentially complex overall pharmacological response of the whole extract depending on the amount of alkaloids present. The binding affinities for mitragynine and 7-hydroxymitragynine at κ- and δ-opioid receptors as partial competitive antagonists has been reported in functional assays as much weaker (κ-opioid receptor: K_i=772 nM for mitragynine and K_i=188 nM for 7-hydroxymitragynine; δ-opioid receptor: K_i>10 μM for mitragynine and K_i=219 nM for 7-hydroxymitragynine). Mitragynine has been investigated in non-opioid receptor binding studies and has shown affinity for α_2-adrenergic, adenosine A_{2a}, dopamine D_2, serotonin 5-HT_{2C}, and 5-HT_7 receptors although it remains unclear if this activity is agonistic or antagonistic [11, 14]. Both *in vitro* and *in vivo* studies confirmed that the analgesic effects of mitragynine are reversible with the administration of naloxone, an opioid-receptor antagonist [15].

7. Known/reported adverse effects, toxicology (both general and specific to organ systems as applicable)

The most common adverse effects with the use of Kratom are nausea, vomiting, constipation, stomach upset, and either drowsiness/dizziness or irritability/agitation [6, 9]. Dry mouth, sweating, sedation, and tachycardia have been reported in doses above 8g. Intrahepatic cholestasis and hepatic liver enzyme elevation has been reported with chronic and frequent use (one month or longer) of Kratom [16]. Liver function returned to normal after cessation of Kratom use. Withdrawal

symptoms associated with Kratom cessation are dose-dependent and may include decreased appetite, diarrhea, agitation, sedation, insomnia, hallucination, changes in heart rate and blood pressure, and seizures [2, 17]. Respiratory depression and hemorrhagic stroke which were reported in fatalities involving Kratom could not be casually linked to the ingestion since they also involved other drugs and/or medications.

8. Known and suspected drug interactions

To date several case studies of drug interactions with Kratom have been reported that relate to its CNS depressant effects. Both additive and synergistic effects are observed if Kratom is used with benzodiazepines, barbiturates, alcohol, opioids, antidepressants, anxiolytics, and other CNS-active drugs [18]. Because of unknown routes of metabolism, specific CYP enzyme interactions remain unknown but caution is advised if Kratom is used in combination with drugs that are substrates of CYP isoforms 1A2, 2C19, 2D6, and 3A4. For a list of general known clinically relevant CYP substrates (not specific to Kratom interactions) see https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#table3-1. Few case reports indicate that some drugs (quetiapine, modafinil) may interact with Kratom although it remains unknown if this can be attributed to a CYP interaction [2, 19]. *In vitro* studies have shown that Kratom and mitragynine are inhibitors of the multi-drug transporter P-gp that may lead to increased concentrations of a range of drugs that are substrates for this transporter [20]. It is not known to what degree these metabolic interactions are clinically relevant.

9. Risks for misuse, abuse, and dependence to Kratom; withdrawal symptoms

Kratom poses a risk for dependence development if consumed in higher doses (more than 5g/dose and more than 3 times/day) on a frequent basis and does present with withdrawal symptoms. The risk of dependence development appears to be higher if the extract is used for harm reduction to mitigate opioid and illicit drug withdrawal or for self-treatment of pain [5, 12, 21]. Case reports of pregnant mothers who used Kratom giving birth to newborns presenting with signs of neonatal abstinence syndrome (NAS) similar to opioids warrants advising against the use of the supplement in this population [22]. Withdrawal symptoms are mild compared to opioids with anxiety, diarrhea, pain, insomnia, restlessness, mood changes, tension, anger, and nervousness presenting. The symptoms may last from 3-10 days following the last dose and withdrawal symptoms can be treated with short-term buprenorphine-naloxone substitution therapy [23, 24].

10. Potential lab values in diagnostic and differential evaluation

There are currently no standard laboratory procedures for the measurement of Kratom or its metabolites in a clinical setting. Methods for the measurement of mitragynine have been described in the scientific literature and a few forensic laboratories have implemented them as part of their screening and confirmatory testing [25, 26]. It has been difficult to link blood concentrations of mitragynine to impairment or toxicity given the wide range of variability with the ingestion of Kratom preparations and undetermined mitragynine levels. Reports of mitragynine blood levels vary from 0.02 to 0.24 µg/g in fatalities (often in combination with other drugs) but also 0.0194 to 0.158 µg/g in subjects who did not experience any serious side effects [12]. Hepatotoxicity indicated through elevated levels of bilirubin, alkaline phosphatase (ALP), and alanine aminotransferase (ALT) have been reported with chronic high doses of Kratom in individuals who take other medications that are potentially hepatotoxic indicating a potential drug interaction [16]. This has not been observed if unadulterated Kratom is taken alone.

11. Treatment approaches, triage, intermittent, and long-term intervention

Presentation of Kratom overdoses can be varied and should be treated symptomatically. In general, patients may be tachycardic and may present with respiratory depression. If seizures are present, a benzodiazepine such as lorazepam (Ativan®) is likely going to be effective. A trial dose of naloxone (Narcan®) has shown to be effective in reversing respiratory depression [27]. Fluid resuscitation is advised in cases of gastrointestinal symptoms such as vomiting, diarrhea, or constipation. In an acute overdose with suspected polysubstance exposure, laboratory values for CBC, electrolytes, ethanol, and a drug screen should be drawn. If possible, the patient should be asked about any other co-ingested substances, licit or illicit, that can cause a complex presentation and require appropriate intervention.

12. Literature

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