

Kratom Consumption can be Addictive and have Adverse Health Effects

Martin Hofmeister^{1*}

¹ Department Food and Nutrition, Consumer Centre of the German Federal State of Bavaria, Munich, Germany

* **Corresponding author:** Martin Hofmeister, Department Food and Nutrition, Consumer Centre of the German Federal State of Bavaria, Mozartstraße 9, D-80336 Munich, Germany
Email: hofmeister@vzbayern.de

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Abstract

Kratom, also known as herbal speed, is the powdered leaves of the Asian kratom tree (*Mitragyna speciosa* Korth). The consumption of kratom powder or kratom tea for diarrhea, inflammation, fever, and pain, but also for anxiety and depression is based on traditional experiences from East Asian herbal medicine.

Pharmacologically, kratom is an intoxicant or narcotic. In low doses, the leaves have a stimulating effect, in high doses, they are depressant and psychoactive like opioids. There is a steadily increasing popularity of the herbal drug kratom and its psychoactive compounds mitragynine and 7-hydroxymitragynine around the world. To date, no randomized controlled human intervention study has evaluated the safety and efficacy of kratom ingestion. In addition, there are increasing reports of kratom-associated adverse effects including herb-induced liver toxicity and nephrotoxicity, cardiovascular and neurological symptoms, and withdrawal syndrome.

The still unsatisfactory lack of regulatory control and easy availability via internet providers will continue to increase kratom use in many countries. Clinicians should be aware that kratom use can be addictive and have potentially serious side effects. It is important to determine the consumption of dietary and herbal supplements when taking the patient's medical history.

Keywords: Kratom, Mitragynine, Adverse effects, Herbal drug.

Introduction

Kratom, also known as herbal speed, is the powdered leaves of the Kratom tree (*Mitragyna speciosa* Korth.) that grows in Southeast Asia countries such as Thailand, Malaysia, Indonesia, Philippines, Papua New Guinea, and Vietnam.¹ Other names for this plant-based substance, which belongs to the Rubiaceae family, are biak-biak, ketum, ithang, thom, maeng da, or mambog. The Kratom tree grows to a height of about 4-16 m and has green, oval leaves, and yellow flowers. The leaves of the plant are offered as tea, powder, extracts, liquids, and capsules mainly via the internet. Exotic "health-promoting" plants in food supplements are booming and lead to an uncritical consumption of such products by consumers. But "natural" does not necessarily mean "safe"! No matter how natural they appear: Plants and plant extracts can contain harmful substances. Only a few important plants have been scientifically evaluated for their harmfulness.²

Kratom background

The consumption of kratom powder or kratom tea for diarrhea, inflammation, fever, and pain, but also for anxiety and depression is based on traditional experiences from East Asian herbal medicine.³ Some strains are said to have a euphoric effect. Pharmacologically, kratom is an intoxicant or narcotic. In low doses (1-5 g), the leaves are said to have a stimulating effect (similar to coca), in high doses, about 5-15 g of dried leaves, they are depressant and psychoactive like opioids.⁴ The effects of chewing or smoking kratom kick in after just 5-10 minutes. There is a risk of physical and psychological dependency (risk of addiction) with regular use at a higher dose.⁵ To date, no randomized controlled human intervention study has evaluated the safety and efficacy of kratom ingestion.^{2,6} The kratom seller or manufacturer alone is responsible for safety. But when he's abroad, it's difficult to hold him accountable. Regardless of its use in Asia, kratom has become increasingly popular over the past two decades in

America, Europe, and Australia.² It is estimated that there are at least 10 to 16 million regular kratom users in the United States.^{3,7} In addition, reports of kratom abuse among adolescents have been published.⁸

Psychoactive kratom alkaloids

Kratom contains over 45 plant alkaloids in very different concentrations, there are no standardized compositions of kratom preparations, so the effect is uncontrollable. The psychoactive compounds mitragynine, 7-hydroxymitragynine, speciociliatine, speciogynine, and paynantheine which act on mu, delta, and kappa opioid human receptors, represent the largest proportion in terms of quantity. In addition, these major indole alkaloids also activate adrenergic (alpha1 and alpha2 receptors), serotonergic (5-HT1A and 5-HT2A receptors), and dopaminergic (D1 and D2 receptors) neurotransmitters in the brain, even at low doses.^{1,5,7} Both main kratom alkaloids, mitragynine, and 7-hydroxymitragynine, have also been shown to inhibit P-glycoprotein-mediated efflux transporters, suggesting the potential for drug-drug interactions with the transporter substrates.¹ Because of its psychoactive effects, kratom is also often advertised as a natural, safe, effective, and legal opioid substitute for methadone and buprenorphine.⁵ Under no circumstances should consumers forego necessary medical treatments - even if it is claimed that a botanical preparation such as kratom could replace them. It is important to talk to a doctor first so as not to take any unnecessary risks. In addition, there is a lack of scientifically valid data on dose-response relationships or the effects of long-term kratom use.²

Kratom-drug interactions

Furthermore, clinically serious drug interactions of kratom and alcohol, opioids, benzodiazepines, and others should not be underestimated by consumers and medical professionals. Kratom alkaloids stimulate the toxicity of pharmacologically active substances via modulation of drug-metabolizing enzymes, in particular cytochrome P450 (e.g. CYP2D6 inhibition), P-glycoprotein, and uridine diphosphate glucuronosyltransferase.^{3,5,9} For example, kratom in combination with high doses of

caffeine can lead to high blood pressure. And the combination with alcohol increases the calming effect, even to the point of shortness of breath. Consumers should generally exercise caution when using plants and plant preparations if they are chronically ill and/or need to take medication regularly. There is still far too little information about the interaction of kratom products with other pharmaceuticals.

Kratom-associated adverse events

Reports of kratom-associated adverse effects including constipation, loss of appetite, herb-induced liver toxicity and nephrotoxicity, cardiovascular and neurological symptoms, and withdrawal syndrome are increasing worldwide (Table 1).^{2,3} And numerous kratom-related deaths have even been reported.^{7,36} In addition, kratom products with massive disease-causing multiple serotypes of salmonella contamination (such as Thompson, Okatie, Heidelberg, Weltevreden, and Javiana) have been found again and again in recent months.³⁷ Some products also contained potentially hazardous high levels of the toxic heavy metals nickel (0.73–7.4 µg/g raw kratom product), lead (0.25–1.6 µg/g), iron (187–850 µg/g), and chromium (0.21–5.7 µg/g). Trace levels of other nephrotoxic metals such as arsenic, cadmium, and mercury were also detectable in kratom supplements.³⁸⁻⁴⁰ Recently, Fleming et al. found in commercially available kratom tea samples manganese levels up to 20 times higher than the tolerable upper intake of 11 mg/day, and as is well known, a longer-term overexposure to manganese can lead to Parkinsonian symptoms (“manganism”).⁴¹ Kratom is a potent drug with serious side effects but without regulatory safety testing and permits.

Legal position

In various countries such as Australia, Denmark, Finland, Italy, Israel, Latvia, Lithuania, New Zealand, Poland, Romania, Russia, Sweden, Switzerland, Turkey, United Kingdom, and in some US states (e.g. Alabama, Arkansas, Indiana, Rhode Island, Tennessee, Vermont, and Wisconsin) kratom is one of the substances to be controlled, so it is not a legal food supplement or possessing kratom is strictly illegal.^{3,4,37,39} In 2021, for

example, U.S. Marshals on behalf of the U.S. Food and Drug Administration (FDA) seized and destroyed over 34 tons of kratom powder and 207,000 packages of dietary supplements containing kratom from Florida manufacturers.⁴²

Kratom is also illegal in most Asian countries. In Brunei, Cambodia, Indonesia, Japan, Laos, Malaysia, Myanmar, Philippines, Singapore, South Korea, and Vietnam it is illegal to possess, buy or sell kratom.^{4,39} In the native country of Thailand, possession, and consumption had been banned since 1943. Since August 2021 there has been a separate law for the use and control of kratom. It is now

legal to grow kratom, and sell and consume the leaves. However, the sale and consumption of concentrates made from the leaves are still illegal. Sale to persons under the age of 18 and pregnant women, online, in schools, and parks is prohibited.

In October 2021, the Expert Committee on Drug Dependence (EDCC) of the World Health Organization (WHO) evaluated kratom's health and adverse effects but did not include it in the United Nations list of internationally controlled substances. However, kratom remains on the list of substances under surveillance by the WHO ECDD.⁴³

Table 1. Recent documented reports of adverse effects associated with kratom use

Adverse events and toxicities	References
Liver injury	Aldyab et al. 2019, ¹⁰ Fernandes et al. 2019, ¹¹ Ahmad et al. 2021, ¹² Botejue et al. 2021 ¹³
Kidney injury	Antony et al. 2019, ¹⁴ Khan et al. 2021, ¹⁵ Sangani et al. 2021, ¹⁶ Jasim et al. 2022, ¹⁷ Tobarran et al. 2022 ¹⁸
Hyperkalemia	Sangani et al. 2021, ¹⁶ Maria-Rios et al. 2022, ¹⁹ Torres-Ortiz et al. 2022 ²⁰
Tachycardia	Eggleston et al. 2019, ²¹ Post et al. 2019, ²² Davidson et al. 2021, ²³ Leong Bin Abdullah et al. 2021 ²⁴
Hypertension	Post et al. 2019, ²² Davidson et al. 2021, ²³ Leong Bin Abdullah et al. 2021 ²⁴
Cardiac arrest	Abdullah et al. 2019, ²⁵ Eggleston et al. 2019, ²¹ Wolfer et al. 2020, ²⁶ Sheikh et al. 2021 ²⁷
Seizures	Eggleston et al. 2019, ²¹ Demick et al. 2020, ²⁸ Burke et al. 2021, ²⁹ Halim et al. 2021, ³⁰ Hartley C 2nd et al. 2022 ⁵
Coma	Eggleston et al. 2019 ²¹
Agitation/irritability	Eggleston et al. 2019, ²¹ Post et al. 2019, ²² Davidson et al. 2021 ²³
Drowsiness/lethargy	Eggleston et al. 2019, ²¹ Davidson et al. 2021 ²³
Vomiting	Eggleston et al. 2019, ²¹ Zuberi et al. 2019, ³¹ Singh et al. 2020 ³²
Withdrawal symptoms	Eggleston et al. 2019, ²¹ Stanciu et al. 2019, ³³ Wright et al. 2021, ³⁴ Smith et al. 2022 ³⁵
Neonatal Abstinence Syndrome	Wright et al. 2021 ³⁴

Conclusion for the clinical practice

Currently, the FDA, Centers for Disease Control and Prevention (CDC), National Institute on Drug Abuse (NIDA), and Drug Enforcement Administration (DEA) in the United States, as well as the European Food Safety Authority (EFSA), are actively evaluating all available scientific information on this international health concern and continue to caution consumers against using products containing kratom or its psychoactive compounds mitragynine and 7-hydroxymitragynine.² The still unsatisfactory lack of regulatory control and easy availability via internet providers will continue to increase

kratom use in many countries.^{2,6} Extensive pharmaceutical law necessary studies on the safety and dosage of kratom products are missing (not to mention the missing standardized compositions of kratom preparations). Therefore, based on the available evidence, this supposed "miracle herb" should also not be recommended by clinicians for pain patients to use as an analgesic or to treat psychiatric comorbidities.⁴⁴

Clinicians should be aware that kratom use can be addictive and have potentially adverse health effects. It is fundamentally very important to determine the consumption of dietary and herbal supplements when

taking the patient's medical history - preferably at every doctor's appointment.

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Competing interests

The author declares that he has no competing interests.

Abbreviations

None applicable.

Author's contribution

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