DOI: 10.4149/BLL_2023_142

Bratisl Med J 2023; 124 (12)
896 – 902

REVIEW

Pharmacology and toxicology of kratom

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ABSTRACT
The term kratom is commonly used for both Mitragyna speciosa and herbal products prepared mainly from leaves. Kratom is well known as a drug that can serve as a less toxic and less-addictive pain-relieving substitute for opium, as well as a therapy for hypertension, cough, and diarrhea. Its major alkaloid, mitragynine, also deserves concern. However, most people use kratom as a psychological stimulant, which carries a risk of addiction associated with negative social and health impacts. This paper reviews basic facts about kratom and its potential use in pharmacology, pharmacokinetics, and pharmacokinetics of its major alkaloid mitragynine *(Tab. 3, Fig. 1, Ref. 87)*. Text in PDF *www.elis.sk*
KEY WORDS: 7-hydroxymitragynine; alkaloid; anesthetics; antitussive; drug; mitragynine*; Mitragyna speciosa;* addictive substance; opioid receptor.

Introduction

Psychoactive substances are chemicals or compounds consumed for their psychoactive properties. Some of the substances can be distributed under some conditions, while others are banned. The regulations in particular states are outcoming from international conventions like the United Nations Single Convention on Narcotic Drugs of 1961 and amended by the 1972 Protocol, Convention on Psychotropic Substances of 1971, Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988, and other related regulations (1–5). Psychoactive substances may pose health and social threats similar to those associated with better-known controlled substances and often appear in the same broad chemical classes such as opioids, benzodiazepines, stimulants, etc. (6).

Many social and ethical issues surround the use and abuse of addictive substances such as drugs, cigarettes, and alcohol. These issues are particularly complex due to conflicting values on substance use within modern societies. Values can be influenced by multiple factors, including social, religious, and personal views. Substance abuse is a pattern of compulsive substance use marked by recurrent significant social, occupational, legal, or interpersonal adverse consequences.

Kratom is a herbal product that can produce opioid- and stimulant-like effects. Many people suffering from social anxiety disorder (or social phobia) have found that kratom relieves their symptoms and helps them be much more sociable. Additionally, kratom increases their confidence, making them more willing to socialize. In some countries, marketing of kratom was impacted by the restriction and the users of kratom can find themselves close to the very edge of what is legally permissible (7). The current opinion on kratom is not singular. While some states tolerate it and do not consider the sale of kratom as a risk, others strongly regulate or disapprove marketing of kratom and enlist it as an addictive substance (8–15).

This review focuses on the topic of kratom, its pharmacological relevance, toxicological impact, and its role as a psychoactive substance. The current literature is searched and discussed. The conclusions are an outcome of recent articles on kratom research.

Kratom plant and its growing

Kratom trees are native to the tropical and subtropical regions of Southeast Asia and can grow very tall in their natural habitat. They are notoriously difficult to propagate and can be started from seed or cuttings, both of which have relatively low success rates. Kratom can be found growing wild and produced solely. While it is possible to grow kratom outside its original region, it can be quite difficult to do so. However, some studies are focused on the growth of kratom outside its original region. In such a case, it frequently needs to be grown in a greenhouse (16). The key to success when growing kratom is to understand the ideal conditions under which this plant thrives in its natural environment and then adjust to match these conditions as much as possible. Kratom prefers warm temperatures between 20 and 30 °C, nutrient-dense soil with humus, soil pH balance between 5.5 and 6.5, and full-to-partial sun exposure (17, 18).

The proper botanical name of the common kratom tree is *Mitragyna speciosa*, but there are also some other species of the

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Acknowledgements: We extend our sincere gratitude for the long-term organization development plan for medical concerns WMD II, (DZRO-FVZ22-ZHN II).

Tab. 1. Basic facts about kratom tree *Mitragyna speciose.*

Proper biological name	*Mitragyna speciosa*
Common name	Kratom
Family	*Rubiaceae*
Region of natural occurrence	Southeast Asia
Type of plant	Tropical evergreen tree with height up to 30 m
Demands on the environment	hot temperatures, nutrient-dense soil with humus, acidic soil pH, and full to partial sun exposure
Species related to the genus	*M. ciliata, M. diversifolia, M. hirsuta, M. inermis, M. javanica, M. parvifolia, M. rotundifolia, M. rubrostipulata, M. speciosa, M. stipulosa, M. tubulosa*

Mitragyna genus including *M. ciliata*, *M. diversifolia*, *M. hirsuta*, *M. inermis*, *M. javanica*, *M. parvifolia*, *M. rotundifolia*, *M. rubrostipulata*, *M. speciosa*, *M. stipulosa*, and *M. tubulosa* (19). While *M. speciosa* occurs in Southeast Asia, some species of the Mitragyna genus can also be found in the tropical and subtropical regions of Africa.

The kratom tree *M. speciosa* is a tropical evergreen tree that can grow to a height of 30 meters, but most of the trees are lower. The color and shape of its leaves and bark resemble most other tropical trees: smooth, with flat bark and glossy leaves that point to the tip. Also, the kratom tree has a diverse branch pattern, which helps it gain maximum sun exposure. For the most part, the leaves that are harvested from a kratom tree are red-veined. Younger leaves can have white veins while the veins of middle-aged trees can be green.

Kratom is a member of the *Rubiaceae* family of plants, making it a close relative of the coffee plant (*Coffea* species). Some other plants that are related to kratom and have been used in traditional medicine or have economically important products including coffee (*Coffea* species), quinine (*Cinchona* species), ipecac (*Carapichea ipecacuanha)* and gambier (*Uncaria gambir*). The aforementioned facts about the kratom tree are summarized in Table 1.

Kratom as a drug

The term kratom is commonly used for *M. speciosa* and also for the herbal product prepared from the leaves (20). Therefore, some misunderstanding can occur regarding the term kratom, some authors can use the term kratom even for other species of the Mitragyna genus. The leaves are harvested and then processed by drying, fermenting, and grinding to provide the drug in the form of powder (the most common form). Drink-like concoction, tea or extracts are also known (less common form). The color of the vein can indicate the leaf's maturity. For example, a red vein typically indicates that the leaf is mature, while a white vein indicates that the leaf is young. As a result, different colors of kratom may have varying chemical components. The leaves have to be dried to preserve their alkaloid content. After the leaves are harvested, they are homogenized by crushing or grinding into a fine powder that can be used directly or stored. Vacuum-sealed bags are common for the purpose of kratom storage. Different powders can be produced depending on the length and specifications of the drying or homogenization process. Kratom powder comes in four basic colors: red, white, green, and yellow. These colors come primarily from the color of the central vein present in the kratom leaves, but other conditions can also influence the color of powder. For example, white kratom strains are typically made by drying them indoors without exposure to UV light, while yellow kratom is associated with a fermentation process. Kratom can also be extracted by organic solvent resulting in solutions of various colors depending on the material used and the extraction procedure (21).

Kratom has been used in traditional medicine for a long time to treat pain and diarrhea. In addition, it acts as a stimulant, and is even used as a substitute for opium (22–24). Its effect is dose dependent. While low doses have a stimulatory effect, rendering the user more energetic a higher dose can cause euphoria. The opposite effect, i.e., sedation, can be expected when the dose of kratom is extremely high. In such a case the users become quiet and somnolent. The effects caused by kratom arise within minutes after intake and subside within few hours (25).

Probably the most well-known use of kratom is related to the psychical stimulation that is mediated by the interaction of major alkaloids (specific alkaloids are described in the next chapter) with opioid receptors. Opioid effects and psychoactive stimulation are the main reasons why kratom can be considered an addictive drug (26–28). In addition to stimulation of opioid receptors, the alkaloids contained in kratom can also interact with adrenergic and serotonergic receptors (29, 30). The question of kratom's hazardousness as a substance of abuse and psychoactive drug remains unanswered, which is also the reason why some states tolerate its sale while others impose restriction on it. While some studies indicate that there is no threat of significant impairments for kratom users (31), other studies suggest kratom to have a negative impact on the quality of life (32). Uncontrolled kratom intake for

Tab. 2. Basic facts about kratom use as a drug.

Source of substance	Leaves of M. speciosa; dried, fermented, grinded to a powder (most common) or prepared as a concoction (less common)
Types of powder kratom	Red, white, green, and yellow, depending on the color of the central vein and manufacturing conditions
Use as a drug	Psychical stimulation, pain relief, substitute for opium, therapy of hypertension, cough and diarrhea
Symptoms of kratom overdose	Restlessness, tremors, convulsions, hypertension, tachycardia, bradycardia, cardiac arrest, mydriasis, miosis – the final effect depends on various conditions including dose
Kratom's physical withdrawal symptoms	Muscle spasms and pain, sleeping difficulty, watery eyes and nose, hot flashes, fever, diarrhea, problems with appetite
Kratom's psychological withdrawal symptoms	Restlessness, tension, sadness, anger and nervousness

a long period leads to psychological and physical addiction, and opioid-like withdrawal syndrome will occur when kratom intake is discontinued (33–35). As described in the study by Trakulsrichai et al, the withdrawal syndrome includes myalgia, insomnia, fatigue, and chest discomfort (36). In another study, 293 regular kratom users were examined and their withdrawal syndromes were observed (37). The users took kratom regularly for at least 6 months and received at least three glasses of kratom drink with an approximate content of 79 mg of mitragynine and a total average mitragynine dose of 277 mg. About half of the probands developed severe problems, while around 45 % showed moderate addiction. Muscle spasms and pain, sleeping difficulty, watery eyes and nose, hot flashes, fever, diarrhea, and problems with appetite were reported as physical withdrawal symptoms. Restlessness, tension, sadness, anger, and nervousness were reported as common psychological withdrawal symptoms. The withdrawal syndromes can be improved, e.g., with buprenorphine-naloxone medication (38, 39).

Pain relief is another known effect self-reported by kratom users. Kratom has not been fully tested for this purpose yet; however, some minor clinical tests were performed successfully, and pain relief effects were confirmed. The volunteers in a study by Vicknasingam and colleagues received kratom or placebo and were tasked to undergo the cold pressor test. The time between the onset of pain to the withdrawal of the hand from the ice bath was measured (40). This experiment proved a significant increase in pain tolerance one hour after kratom intake. Kratom can also be used in therapy for hypertension, cough, and diarrhea (41, 42). Staving off fatigue is another purpose of its use (43, 44).

While there may be a potential for addiction to kratom and kratom is taken for an addictive substance, the stimulation of opioid receptors can make it a less addictive substitute for opiates. Moreover, there are even studies on the potential of kratom to mitigate alcohol abuse (45, 46). People report using kratom to manage withdrawal symptoms and cravings, especially related to opioid use (47). There is also evidence suggesting that some opioid polydrug users used kratom as a means to abstain from opioids (48). However, it is important to note that kratom is not generally approved for the purpose, for instance, by the regulatory bodies such as US Food and Drug Administration, European Medicines Agency or National Medicinal Products Administration (China); As a result, the use of kratom for mitigation of addiction lacks worldwide acceptance, and it is more commonly employed as a traditional local medicament or uncertified preparation for self-medication.

Kratom is not a highly toxic substance, but its overdose can be harmful and even fatal. Cases of death due to kratom are not rare. For example, in the United States, the total numbers of deaths due to kratom overdosing or kratom addiction reached 44 and 91 in 2018 and 2019, respectively (49). Graves et al. analyzed 3,484 adult kratom exposures based on data from the American Association of Poison Control Center's National Poison Data System for the years 2014-2019 (50). The incidence of adverse reaction to kratom, including the neurological and cardiovascular clinical effects among probands in age groups of 18–59, 60–69 and over 70 years reached 9.6 %, 12.3 % and 20 %, respectively. There were 23 deaths recorded in the group of 3,484 adults, which represents a mortality rate of 0.66 %. In another study based on the National Poison Data System, the incidence of clinical effects among kratom users was 86.1 %, of which agitation/irritability and tachycardia were the most common symptoms (51). Restlessness, tremors, and convulsions are typical symptoms of serious overdosing with kratom (52). Hypertension, tachycardia, bradycardia, cardiac arrest, cardiac arrythmia, mydriasis, and miosis are other symptoms revealed in various case reports (53–56). As seen from the case reports, kratom can exert oppose effects depending on individual conditions, kratom dose, and period of kratom intake. On the tissue level, acute cholestatic liver injury was recorded in some case reports (57–59). In a study by Mata and Andera, the concentration of mitragynine in the blood, the major alkaloid of kratom, was determined in cases of fatal poisoning during the period of 2017–2018 (60). They reported that postmortem central blood concentrations ranged from 10 to 4,310 ng/l with a mean of 625 and a median of 123 ng/ml. Subsequent facts about kratom use as a drug are summarized in Table 2.

Biologically active substances in kratom

The biological effects of kratom are caused by a group of alkaloids present in the herbal material. Their content and exact ratios of particular substances may differ between samples. For instance, the young leaves contain a higher content of biologically active substances compared to the old foliage (61). Currently, it is known that more than 40 biologically active alkaloids, including indole and oxoindole, can be found in the leaves of *M. speciosa* (62). The number may be even higher as indicated by some studies on monoterpene indole alkaloids where more than 50 particular oxoindole secondary metabolites were identified (63). In addition to alkaloids, kratom contains also flavonoids, triterpenoid compounds, saponins and tannins (64). In a study on *M. speciosa* seeded in North America, identified were alkaloids such as ajmalicine, corynantheidine, isomitraphylline, mitraphylline, paynantheine, isocorynantheidine, 7-hydroxymitragynine, mitragynine, flavonoid epicatechin, a saponin daucosterol, terpenoid saponins quinovic acid 3-O-beta-D-quinovopyranoside, quinovic acid 3-O-beta-D-glucopyranoside, and glycosides 1-O-feruloyl-beta-D-glucopyranoside, benzyl-beta-D-glucopyranoside, 3-oxo-alpha-ionyl-O-beta-D-glucopyranoside, epivogeloside, roseoside, vogeloside (65). In another experiment, the total content of alkaloids was analyzed and found that mitragynine represents 66 % of the alkaloid content of leaves of *M. speciosa* while 7-hydroxymiragynine, paynantheine, speciogynine, and speciociliatine represent 2.0 %, 8.6 %, 6.6 % and 0.8 %, respectively (66). The structures of selected alkaloids and other secondary metabolites contained in kratom are shown in Figure 1.

The alkaloid mitragynine is the major substance responsible for most of the biological effects attributed to kratom. It is an alkaloid based on indole structure and with a quite high content in the leaves of *M. speciosa*. The mitragynine in dry leaves varies approximately between 0.3 and 3.5 % w/w with a peak in June-to-August period and some samples from trees in Thailand can even reach a con-

tent 5 % w/w (67). Mitragynine in range of 7.5–27 mg/g (0.75–2.7 % w/w) was reported in another study on kratom leaves from various regions of Thailand (17). The main physiological impact of mitragynine is through opioid receptors. The interaction with mu, delta and kappa opioid receptors was documented (68–70). The mechanism of action is not fully understood. Some experiments report that mitragynine acts as an agonist of mu receptors, while it is an antagonist of delta and kappa opioid receptors (71). The interaction with the mu opioid receptor is quite strong and the equilibrium constant is around 161 nmol/l (72). Mitragynine can also interact with other regulatory pathways. An association with

Tab. 3. Basic facts about mitragynine as a major active substance in kratom.

Specification	Value	References
Content of mitragynine in dry leaves of M. speciosa	0.3-3.5 % w/w, can even exceed 5 % w/w	(67)
Major target receptors	Agonist of mu, antagonist of delta and kappa opioid receptors	(68-70)
Other targets	Inhibition of P450 2C9, 2D6 and 3A4, enhancing of dopamine transporter and dopamine receptor regulating factor genetic expression	(73,76)
Major detoxification of mitragynine	Cytochrome P450 3A	(74,75)
LD50 for mice	Intravenous application: 27.8 mg/kg; per oral application: 477 mg/kg	(77,78)
Time for reaching the peak concentration in plasma after oral intake	0.83 hours (human volunteers); 30 minutes (beagle dogs)	(80,81)
Volume of distribution	38 l/kg (human volunteers), 6.3 l/kg (beagle dogs)	(80,81)
Half-life (human volunteers; blood)	23 hours	(80)
Clearance (beagle dogs)	1.8 l/h/kg	(81)

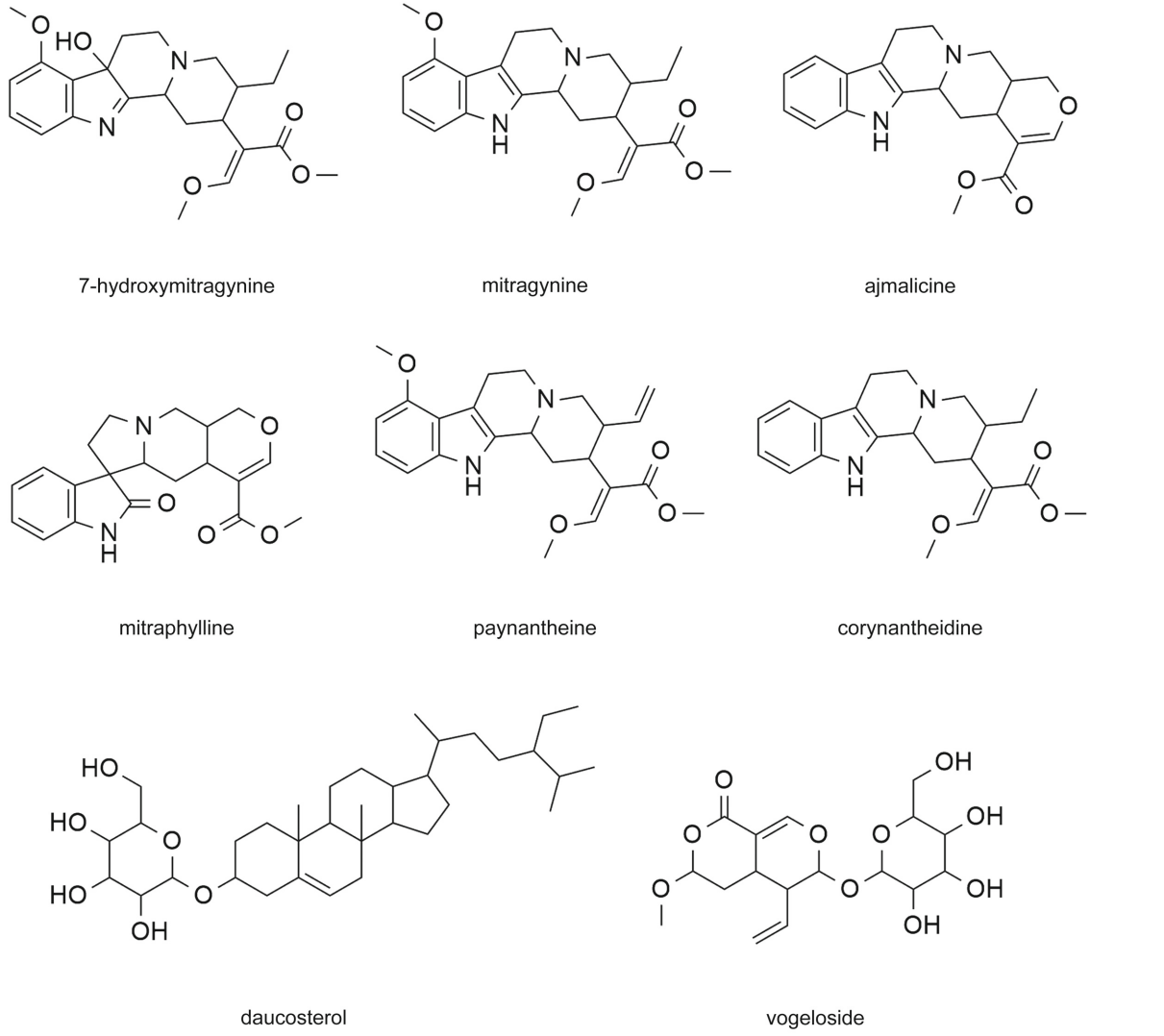

Fig. 1. Structures of selected substances presented in kratom.

dopamine receptors was discovered, probably based on enhancing the dopamine transporter and dopamine receptor regulating factor genetic expression (73). Also, mitragynine metabolism is not fully understood. It is oxidized in the liver to 7-hydroxymitragynine on cytochrome P450 3A (74,75), but there are also findings that some P450 isoenzymes, namely 2C9, 2D6 and 3A4, can be inhibited by mitragynine and mitragynine influences the metabolism of the other alkaloids or drugs by this way (76). The toxicity of mitragynine has not been fully revealed yet, but it appears that it is a low-toxic substance. In an experiment on laboratory mice, the median lethal dose, LD50, for orally applied mitragynine was equal to 477 mg/kg and the therapeutic index for pain reduction and withdrawal signs was equal to 21 while the therapeutic index 3 was reached for a crude alkaloid extract of *M. speciosa,* yielding an LD50 value of 591 mg/kg (77). Intravenous application of mitragynine results in much higher toxicity. In an experiment on laboratory mice, the LD50 value of mitragynine was 27.8 mg/kg when administered intravenously, similar to the LD50 for 7-hydroxymitragynine, which is 24.7 mg/kg (78). These data indicate that mitragynine is biologically active but less toxic compared to other substances contained in kratom, but these conclusions need to be further corroborated by more detailed experiments. The toxicity of mitragynine in humans can be estimated on the basis of clinical reports. A team of Schmitt and co-workers studied 35 reports on kratom overdosing in Northern Nevada between years 2015 and 2020. Out of these reports, 27 cases were identified as having mitragynine playing a significant role (79). They reported on mean blood concentration of mitragynine in victims of kratom overdosing with a contribution of 269 ± 383 ng/ml to the cause of death. The range of mitragynine in the blood was found to be 8.7 to 1800 ng/ml. The pharmacokinetics of mitragynine is known from some studies dealing with basic pharmacokinetic specifications. In a paper investigating regular healthy users, maximal plasma concentration was reached after 0.83 ± 0.35 hours, while the half-life value was equal to 23.2 ± 16.1 hours and the apparent volume of distribution was 38.0 ± 24.3 l/kg for mitragynine administered in the form of kratom tea (80). In an experiment with female beagle dogs that received mitragynine intravenously, the volume of distribution was equal to 6.3 ± 0.6 l/kg and the clearance was equal to 1.8 ± 0.4 l/h/kg (81). The maximum plasma concentration was reached within 30 minutes when the dogs received mitragynine orally. It appears that mitragynine enters the organism faster than 7-hydroxymitragynine, as the latter can reach its peak in blood after oral intake in 15 minutes (82). The basic facts about mitragynine are described in Table 3. The other indole and oxoindole alkaloids presented in kratom exert similarities to mitragynine considering their pharmacokinetics and pharmacodynamics. Namely, 7-hydroxymitragynine is very close to mitragynine in its specifications, or there are at least significant similarities (83-87).

Conclusions

Kratom is a herbal product that contains various biologically active alkaloids. The current opinion on kratom is ambiguous. There are undisputed applications for medicine, and kratom can serve as a drug for pain relief, substitute for opium, and in therapy for hypertension, cough, and diarrhea. However, it can also act as a psychoactive stimulant and there is a risk of developing an addiction associated with negative social and health impacts. The legislation on kratom is also developing as the use of kratom has spread over the world. There are tests on the use of kratom as a drug, but there are also fears about kratom's negative impact on society. Taking into account the pros and cons, kratom would be a helpful drug, but caution is necessary.

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Received June 3, 2023.
Accepted July 12, 2023.