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Assessment of the possible health risks associated with the consumption of botanical preparations of *Mitragyna speciosa* (kratom)

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Abstract

The current report summarises the work performed in the context of the European Food Risk Assessment Fellowship Programme (EU-FORA), which included the evaluation of health risks associated with the consumption of botanical preparations of *Mitragyna speciosa* (kratom). *Mitragyna speciosa* is a tree native to Southeast Asia, where its leaves and preparations of the leaves have been used for centuries, among others, as a stimulant or as a traditional herbal medicine. Preparations of the plant have recently gained increasing popularity in other parts of the world, and are presently also accessible via online platforms, e.g. as food supplements. Kratom has been considered a botanical of possible health concern by the FDA and EFSA, which together with its increasing popularity, makes kratom a subject of international concern. Major alkaloids of the plant, mitragynine and 7-hydroxymitragynine, are agonists of the μ -opioid human receptor and are assumed to be mainly responsible for its psychoactive effects. The aim of the present project was to conduct an assessment of potential health risks associated with oral use of kratom-based preparations. The animal and human data that were evaluated in the course of the current assessment indicate that kratom consumption has the potential to not only lead to adverse neurological effects, including addiction and withdrawal syndrome, but also to elicit distinct organ toxicity with respect to e. g. liver and kidney as target organs. Nevertheless, actual risk characterisation is impeded by considerable uncertainties. Such uncertainties, based on the variability in composition of kratom preparations, insufficient information on dose–response relationships and on limited data on long-term use effects, currently do not allow the derivation of distinct health based guidance values for kratom/kratom preparations. Further information from well-designed studies, conducted with kratom preparations that have been clearly defined with respect to their composition, would be required to enable a more refined risk assessment of this botanical.

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1. Introduction

1.1. European Food Risk Assessment Fellowship Programme (EU-FORA)

The European Food Risk Assessment (EU-FORA) Fellowship Programme, supported by the European Food safety authority (EFSA), aims to train and increase the number of food safety risk assessment experts available in Europe. In this context, mid-career scientists are offered the opportunity to increase their knowledge and experience in food safety risk assessment, by both theoretical and practical training. The EU-FORA fellow participated in the general work programme entitled 'Risk assessment of botanical preparations used in food supplements and fortified foods', that was hosted by the German Federal Institute for Risk Assessment (BfR), Department of Food Safety, Unit of Nutritional Risks, Allergies and Novel Foods. The work programme comprised the elaboration of a detailed scientific monograph by the EU-FORA fellow that was to include the results of a safety assessment of a botanical and its preparations, taking into account the EFSA guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients of food supplements (EFSA, 2009). The final selection of *Mitragyna speciosa* (kratom) for the current safety assessment was made in agreement between the hosting unit and the EU-FORA fellow.

1.2. General background regarding the risk assessment of *Mitragyna speciosa*

Herbal products are often promoted as safe and effective alternatives to synthetic medicines. An increasing interest in products perceived as being natural and the general misperception that natural equals safe and is thus not associated with adverse effects, may lead to uncritical use of such products by consumers. However, in many cases, botanicals and botanical preparations contain active phytochemicals or complex mixtures of phytochemicals, respectively, that may potentially cause adverse effects which in certain cases may even be life-threatening (Di Lorenzo et al., 2015; Marcus and Grollman, 2015). Many of the products containing botanical preparations are sold as food supplements. According to the current regulatory framework in the EU and the EU General Food Law Regulation (EC) No 178/2002, food supplements are regulated as food. Food business operators, manufacturers and suppliers placing the product on the market are responsible for the safety of these products.

Mitragyna speciosa, which is also called kratom, is a tree native to Southeast Asia. Its leaves have been used in the area for centuries as a traditional herbal medicine for the treatment of several illnesses and pain relief, but also by labour workers in order to increase their stamina. The most common traditional way of use is by chewing or by preparing an infusion of the leaves as tea. During the last decade, botanical preparations from *Mitragyna speciosa* have increasingly also been used in other parts of the world, such as in the United States and Europe. They are often being promoted as food supplements – most commonly in the form of powder, pills and capsules or leaf extracts – for the self-treatment of opioid withdrawal, the relief of withdrawal syndrome, for pain management or for recreational purposes. The major alkaloids of the plant, mitragynine and 7-hydroxymitragynine, are agonists of the μ -opioid human receptor and are assumed to be mainly responsible for the psychoactive effects of kratom. The botanical is listed in the EFSA Compendium of botanicals, reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements (EFSA, 2012) and it has also been considered a botanical of concern by the FDA (FDA, 2017). Although kratom use is illegal in some countries in Europe, it is easily available via Internet providers. This increasing popularity and the easy access to it makes kratom a subject of international health concern.

2. Description of work programme

2.1. Aims

The major aim of the work programme for the fellow was to become acquainted with the general principles of human health risk assessment for foods and in this context, to gain more detailed experience in the risk assessment of certain substances used in food supplements and fortified foods, i.e. substances other than vitamins and minerals, that are substances of plant origin (botanicals, botanical preparations and plant secondary constituents). The hands-on experience acquired by

specifically assessing the possible health risks associated with the consumption of *Mitragyna speciosa* and preparations thereof was further aimed to be the basis for the elaboration of a detailed monograph. Moreover, the programme aimed to create a network of food risk assessment experts by building professional connections between the hosting institution, the fellows of the programme and other experts.

2.2. Activities/Methods

2.2.1. Preparation of a monograph regarding the risk assessment of *Mitragyna speciosa*

The purpose of present scientific project conducted by the fellow was to retrieve, evaluate and summarise the current scientific data regarding health risks related to the consumption of kratom, taking into account the available published animal and human data. The risk assessment was performed based on the BfR-Guidance for health assessments (BfR, 2020) as well as on the EFSA 'Guidance on Safety assessment of botanicals and botanical preparations intended for use in food supplements' (EFSA, 2012). For the hazard characterisation, the relevant published toxicological animal studies and human data, including information from observational studies and case reports, were evaluated. To this end, a literature search was performed in PubMed and other scientific databases to identify relevant scientific publications. In addition, websites of acknowledged scientific bodies or national authorities were checked for information regarding kratom.

In behavioural and neurological studies in rodents involving oral subacute (28 days) administration of mitragynine, cognitive impairments of learning and memory function were observed already at a dose of 1 mg/kg bodyweight (Apyrani et al., 2010; Yusoff et al., 2016; Suhaimi et al., 2021). Acute and subacute (28 days) oral administration of *Mitragyna speciosa* preparations (*Mitragyna speciosa* extracts or isolated mitragynine) caused hepatotoxic and mild nephrotoxic effects in rats and mice. Furthermore, neurotoxicity and pulmonary toxicity were observed in rats (28 days) at doses of ≥ 100 mg/kg bodyweight for a methanol extract or isolated mitragynine (Harizal et al., 2010; Kamal et al., 2012; Sabetghadam et al., 2013; Sakaran et al., 2014; Ilmie et al., 2015; Panjaitan and Liridah, 2021).

Currently, human intervention studies are not available and human observational studies in which adverse effects of kratom ingestion were investigated are limited. Following cessation of regular kratom use by humans, dependence and withdrawal syndrome have been observed. Other adverse effects associated with kratom use include liver toxicity and neurological symptoms such as dizziness and drowsiness (Suwanlert, 1975; Ahmad and Aziz, 2012; Saingam et al., 2013; Singh et al., 2018). A large number of human case reports have described signs of intoxication and even death following kratom ingestion. The documented adverse events include herb-induced liver injury, neurological effects (seizures, coma, central nervous system depression, altered mental status, hallucinations, confusion and drowsiness), cardiovascular effects (palpitations, tachycardia, cardiac arrest), withdrawal syndrome, respiratory dysfunction as well as cases of lethal outcome (Alsarraf et al., 2019; Schimmel and Dart, 2020).

2.2.2. EU-FORA Fellowship supporting programme

At the beginning of the fellowship, the fellow was introduced to the activities performed at the Department of Food Safety of the BfR and at the hosting unit (Unit of Nutritional Risks, Allergies and Novel Foods). The fellow obtained experience in the risk assessment of botanicals and botanical preparations by performing a risk assessment with respect to *Mitragyna speciosa* and by the elaboration of the respective monograph. The above work was completed under the guidance and effective supervision which was provided through regular meetings and on site communication with members of the hosting unit. Apart from the practical work at the BfR during the fellowship year, the fellow participated in the following activities described in Table 1. A considerable part of the fellowship programme was carried out remotely, due to the COVID-19 pandemic situation.

Table 1: Supporting activities during the EU-FORA Fellowship programme

	Title	Date
Training modules provided by EFSA	Induction training – Microbiological and chemical risk assessment (virtual)	11–29 January 2021
	Training Module 1 – Risk communication, organised by the German Federal Institute for Risk Assessment (BfR) (virtual)	22–26 March 2021
	Training Module 2 – Emerging risks, organised by the Hellenic Food Authority (EFET) (virtual)	7–14 June 2021
	Training Module 3 – Data collection and reporting, organized by EFSA (virtual)	4–7 October, 2021
	Training Module 4 – Other risk assessments, organized by the Austrian Agency for Health and Food Safety (AGES) (virtual)	22–26 November, 2021
Other training/ workshops	BfR-Summer Academy (virtual event)	16–20 August 2021
	Workshop 'Risk Assessment and Risk Management of Genetically Modified Organisms (GMO)' (BfR)	9 November 2021
Scientific meetings	Poster presentation 'Evaluation of possible health risks associated with consumption of botanical preparations of <i>Mitragyna speciosa</i> (kratom)' at the EUROTOX 2021 Virtual Congress	27 September to 1 October 2021
Other activities	Regular meetings with the Unit of Nutritional Risks, Allergies and Novel Foods of the BfR (virtual and on site)	–
	Regular seminars organised by the Department of Food Safety of the BfR: Food safety related scientific presentations on current projects of the different department units (virtual)	Twice per month
	Presentation by the fellow of the EU-FORA programme of the results of <i>Mitragyna speciosa</i> risk assessment at the department seminar (BfR)	14 December 2021
	Participation in international socialising events organised by the International Affairs team of the BfR	–

3. Conclusions

3.1. Conclusions regarding *Mitragyna speciosa* (kratom) risk assessment

The available animal and human data that were evaluated by the fellow strongly indicate that kratom consumption has the potential to cause a number of adverse health effects, including addiction, associated withdrawal syndrome and other manifestations of toxicity, such as further aspects of neurotoxicity, but also liver toxicity and nephrotoxicity. However, the derivation of any health based guidance values for kratom preparations or constituents thereof and a subsequent concrete risk characterisation are severely impeded by considerable uncertainties, including the variability in composition of kratom preparations, insufficient information on dose–response relationships or on effects of long-term use. Further information, based on well-designed studies that cover different doses and periods of time and have been conducted with preparations clearly specified with respect to their composition, is required in order to reduce uncertainties and enable a more refined risk assessment.

3.2. Conclusions regarding the participation in the EU-FORA programme

During the year of the EU-FORA fellowship programme, the fellow learned general principles of risk assessment and gained experience in the risk assessment of substances and preparations of botanical origin used in food supplements, improving also her skills in the systematic extraction, structuring and evaluation of relevant scientific data. Furthermore, the participation in the EU-FORA programme provided an exceptional opportunity for the fellow to become part of an international experts' network that is expected to be a valuable source of future professional support and to provide a basis for further collaboration.

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Abbreviations

BfR	Bundesinstitut für Risikobewertung (German Federal Institute for Risk Assessment)
EU-FORA	European Food Risk Assessment Fellowship Programme
FDA	Food and Drug Administration