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Risk assessment regarding the use of *Annona muricata* in food supplements

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Abstract

The current risk assessment was performed in the context of the European Food Risk Assessment Fellowship Programme (EU-FORA) supported by EFSA and was intended to evaluate possible health risks associated with the consumption of *Annona muricata* L. (Annonaceae) and derived food supplements. *A. muricata* grows as a tree and is native to the Caribbean and Central America. Preparations made from different plant parts of *A. muricata* (i.e. fruit, leaves, bark, roots) have been used as herbal medicine and are also marketed worldwide as over-the-counter food supplements that have been purported to support general health or to treat a wide range of health conditions, particularly cancer and parasitic infections. However, open questions remain regarding the safety of *A. muricata*-based food supplements, since Annonaceae have been reported to contain potentially neurotoxic compounds, i.e. acetogenins. The assessment conducted within the present fellowship programme shows that substantial uncertainties exist regarding the safe use of *A. muricata*-based supplements. The available data provide indications of neurotoxic potential of certain *A. muricata* preparations. The paucity of adequate studies, particularly related to long-term use of *A. muricata* supplements, currently does not allow the establishment of a safe intake level. Within this technical report a workflow of the project is presented.

Keywords: *Annona muricata* L., annonacin, botanical preparation, food, food supplement, neurotoxicity, risk assessment

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1. Introduction

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

The EU-FORA programme supported by the European Food Safety Authority (EFSA) offers an opportunity to professionals within the European Union (EU) to increase their knowledge and experience in food safety risk assessment (Bronzwaer et al., 2016). The aim of the programme is to contribute to the expansion of the EU's community of scientists working in the field of risk assessment and thus to increase both the pool of experts and to support cooperation with respect to food safety risk assessment activities at both the national and EU levels (Bronzwaer et al., 2016).

The EU-FORA fellow was hosted by the German Federal Institute for Risk Assessment (BfR), Department of Food Safety, Unit of Nutritional Risks, Allergies and Novel Foods. Within the agreed work programme that was entitled 'Risk assessment of botanical preparations used in food supplements and fortified foods', the main task of the fellow was the preparation of a monograph regarding the risk assessment of *Annona muricata* and preparations derived thereof with respect to use in food supplements.

1.2. General background regarding the risk assessment

The use of herbal preparations has gained popularity in industrialised countries as complementary or alternative approach to pharmacotherapy involving synthetic, monosubstance pharmaceuticals (WHO, 2013). With a high demand driven by consumer's health concerns, cultural factors, the belief that herbal preparations are natural and thus safe, and since herbal products are often viewed as being balanced and moderate home remedies, thousands of herbal products, including herbal food supplements, are advertised, marketed and distributed via various channels, including pharmacies, natural herbal shops, online retail stores and social media platforms (Raclariu et al., 2018). Herbal preparations often contain a complex mixture of natural chemicals, the composition of which depends, among others, on plant growth conditions, the part of the plant used for processing and the conditions of processing, i.e. conditions of extraction from the plant. Despite their popularity, the assessment of their safety requires a thorough multidisciplinary scientific investigation and validation of their chemical and biological activities, including potential pharmaceutical, pharmacological and toxicological activities. However, in cases where herbal products are sold as food supplements, surveillance of such herbal products with respect to potential adverse effects (nutrivigilance) remains difficult because these products do not require a medical prescription and are sold as over-the-counter products. Legislative frameworks that take into account monitoring, consistent documentation and evaluation of adverse effects associated with food supplements are not in place in many EU countries.

Herbal products' regulations vary greatly between countries and continents. In the EU/EEA, herbal products fall into two main categories, depending on their primary intent of use: i) 'herbal medicines' that are regulated under medicinal products' legislation and ii) 'herbal food supplements' that are covered by the provisions of food legislation. The European Directive 2002/46/EC defines food supplements as concentrated sources of nutrients or other substances with nutritional or physiological effect whose purpose is to supplement the normal diet. Regarding more specific provisions for nutrients or other substances, the Directive 2002/46/EC so far only regulates which vitamins and minerals may be added to food supplements and which vitamin/mineral substances or compounds may be used. Daily maximum amounts for vitamins and minerals in individual food supplement products have not yet been established at the EU level. With respect to 'other substances with a nutritional or physiological effect', current specific provisions (with only a few exceptions) are lacking as to which 'other substances' may be used in food supplements or regarding daily maximum amounts for individual substances in food supplement products.

Though the quality and safety of herbal food supplements need to fulfil the requirements of food legislation, these are, however, considerably less stringent compared to the medicinal products regulations. Thus, unlike drugs, which must be approved by the competent authorities before they can be marketed, food supplement products do not require premarket review or approval within the EU and their safety and conformity with the food law requirements is under the responsibility of manufactures and suppliers.

Annona muricata L. (Annonacea), known as graviola (Portuguese), guanabana (Spanish), Stachelannone (German) or soursop (English), grows as a tree and is endemic to the warmest areas of the tropics of South and Central America and the Caribbean. In addition, it has been distributed very early to eastern and western Africa, Asia and to south-east China (Wahab et al., 2018). Various

preparations from fruits and other plant parts of *A. muricata* are marketed worldwide as over-the-counter food supplements that are purported to support general health or to treat a wide range of health conditions, particularly cancer and parasitic infections (Badrie and Schauss, 2009; Coria-Téllez et al., 2018). However, open questions remain regarding their safety since Annonaceae have been reported to contain potentially neurotoxic compounds, i.e. acetogenins. *A. muricata* is also 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).

The current risk assessment is intended to evaluate possible health risks associated with the consumption of *A. muricata*-based food supplements, based on available published data.

2. Description of the work programme

The hosting Unit in which the work programme was carried out (BfR Unit Nutritional Risks, Allergies and Novel Foods) has long-standing experience in risk assessment of food supplements and fortified foods. One of the major areas of its research relates to the risk assessment of 'other substances' with specific nutritional or physiological effects, including the safety assessment of secondary plant ingredients and plant preparations.

2.1. Aims

The aims of the work programme were for the fellow to i) gain experience in performing risk assessment of 'other substances' used in food supplements or fortified foods, with a focus on substances of plant origin ('botanicals', i.e. plant preparations and secondary plant compounds); ii) to specifically assess the possible health risks associated with the consumption of *Annona muricata*-based food supplements; and iii) to set up further networking and build professional collaboration with the host institution, as well as with other experts in various fields of food risk assessment.

The activities described below were in line with the aims of the work programme proposed by the BfR.

2.2. Activities/methods

2.2.1. Preparation of a monograph for the risk assessment of *Annona muricata*

Possible health risks associated with the consumption of *A. muricata*-containing food supplements were evaluated based on available published data. Risk assessment was performed following the 'BfR Guidance Document for Health Assessments' (BfR, 2010) as well as the EFSA 'Guidance on Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements' (EFSA, 2009). A detailed monograph on *A. muricata* was prepared, forming the basis for a publication to be submitted to a peer-reviewed scientific journal.

In the course of the training, the fellow gained experience in i) searches in scientific databases and search strategies to identify relevant scientific publications, ii) systematic data extraction from scientific publications, iii) structuring of scientific data, iv) evaluation of scientific data from individual studies as well as from the overall data situation (i.e. assessment of observed effects, identification of toxicological key parameters, characterisation of dose–response relationships), v) methods for derivation of health-based guidance values, vi) identification of potentially sensitive groups and groups at risk, vii) structure and content of risk assessment monographs, and viii) scientific writing.

The corresponding detailed risk assessment report on *A. muricata* is to be submitted for publication in a peer-reviewed scientific journal shortly. Therefore, in the context of the present technical report, the workflow, methodology and results of the risk assessment are summarised in brief in the following:

Scientific databases such as `PubMed/Medline', 'Scopus', 'Google Scholar' and 'Web of Science' were searched in order to retrieve relevant publications, with the last update being in mid-March 2020. Numerous search strategies were used, including different names of the plant species of interest (i.e. '*Annona muricata*', 'soursop', 'graviola') in connection with terms related to the endpoints of interest, as for instance 'adverse effects', 'toxicity' or 'safety'. This represented the basis for identifying scientific evidence provided in peer-reviewed scientific publications in relation to compounds of potential concern contained in *A. muricata*, alongside with toxicological data and studies reporting adverse health outcomes in humans. Additionally, scientific abstracts, reports as well as pertinent evaluations performed by scientific bodies or national and international authorities dealing with food and drug safety were checked as well. Moreover, the key grey literature was considered, including articles published in non-scientific journals, project reports, and other forms of documentation outside of scientific literature.

Data from the literature studies included in the present risk assessment were retrieved, summarised and arranged, based on the following criteria: 1) chemical composition of constituents of *A. muricata* and of the derived herbal preparations, 2) human studies, 3) acute, subchronic and chronic toxicological animal studies, 4) *in vitro* studies, and 5) potential pharmakokinetic and pharmacodynamic interaction.

With respect to constituents of *A. muricata*, about 200 bioactive secondary plant compounds have been isolated and described from *A. muricata*, with the most abundant being annonaceous acetogenins (ACGs), followed by alkaloids, flavonoids and phenols (Leboeuf et al., 2007; Bonneau et al., 2017; Coria-Téllez et al., 2018). ACGs have been proposed to have cytotoxic, antitumoral, antimalarian, antiparasitic, antiviral, antimicrobial or immunosuppressant activities, or as pesticidal agents, and some are well known to be potent inhibitors of the mitochondrial complex I (NADH-quinone-oxidoreductase) in the respiratory chain (Bermejo et al., 2005; McLaughlin, 2008). Among ACGs, annonacin has been identified as the most abundant in *A. muricata* (Yamada et al., 2014; Coria-Téllez et al., 2018).

Several human observational studies were identified (Caparros-Lefebvre and Elbaz, 1999; Chaudhuri et al., 2000; Caparros-Lefebvre et al., 2001; Caparros-Lefebvre and Lees, 2005). These studies suggested an association between the long-term consumption of fruits and infusions made from other plant parts *of A. muricata* (i.e. leaves) and an increased incidence of movement disorders that resembled Parkinson's disease. In one of these studies. the post-mortem neuropathological and biochemical examination of some affected patients showed an accumulation of tau proteins in the midbrain (Caparros-Lefebvre et al., 2001). However, causality in relation to *A. muricata* is difficult to prove and information provided in the observational studies is insufficient in this respect.

Regarding the use of *A. muricata* in food supplements, scientific information from human intervention studies, which might be used for safety evaluation of *A. muricata,* is currently lacking. This represents a major data gap that impedes risk assessment, especially in the case when long-term use of high supplemental *A. muricata* doses is intended. Along these lines, the importance to include a detailed documentation regarding the incidence of adverse effects and measurements of clinical safety parameters in any future intervention studies is underlined.

Among retrieved animal studies, some 'classical' toxicological *in vivo* studies showed that the exposure to annonacin (whether in the form of *A. muricata* extracts or as purified phytochemical), induced serious neuropathologies in rodents (Champy et al., 2003; Lannuzel et al., 2006; Yamada et al., 2014). For instance, after i.v. application of annonacin over 28 days to rats, annonacin accumulated in the brain parenchyma, decreased brain ATP levels, induced neuropathological abnormalities in the basal ganglia and loss of nigral and striatal neurons in exposed animals (Champy et al., 2003). Moreover, following 1-year oral exposure to *A. muricata* fruit juice, increased numbers of neurons with phosphorylated tau proteins in several brain regions were observed in wild-type and human tau protein transgenic mice (Rottscholl et al., 2016). No further toxicological long-term animal studies with *A. muricata* preparations were identified.

In vitro, annonacin extracted from the root of *A. muricata* promoted death of dopaminergic neurons in embryonic rat mesencephalic cultured cells and caused tau protein pathology in cultured rat striatal neurons (Lannuzel et al., 2003, 2006). A high degree of toxicity on Lund human mesencephalic cells was observed after exposure to preparations from marketed dietary supplements containing leaves and stems of *A. muricata* (Höllerhage et al., 2015).

Regarding *A. muricata* preparations that might be used in food supplements, the composition of such preparations may differ considerably, depending, among others, on conditions of plant growth, conditions of harvest, part of plant used, method of extraction and further processing of the preparation. Reliable toxicological data, human studies or toxicokinetic *in vivo* data, however, are currently lacking for specific food supplement products based on *A. muricata* preparations. There is also a lack of reliable *in vitro* and *in vivo* studies with respect to potential interactions between *A. muricata* preparations and conventional drugs.

In cases where relevant information from safety testing is lacking for certain botanicals and thus the data situation does not provide a sufficient basis for a comprehensive risk assessment, it has been suggested by EFSA to follow a presumption of safety approach. This approach implies that for botanicals traditionally consumed as food, it is assumed that intake, i.e. via supplements or fortified foods, that corresponds to the intake via traditional or normal diet does not pose a risk (EFSA, 2014). However, due to the lack of information on traditional or background exposure to *A. muricata* or constituents thereof via food, the application of the presumption of safety approach for the use of *A. muricata* and derived preparations, including preparations marketed as herbal food supplements, is currently not feasible.

In conclusion, risk assessment regarding the consumption of certain *A. muricata*-based food supplement products faces a number of challenges, including the lack of standardisation of composition of *A. muricata* preparations used in food supplements and the lack of information from reliable studies with preparations actually used in food supplements.

2.2.2. EU-FORA Fellowship supporting programme

During the introductory phase of the fellowship, the fellow obtained general information on risk assessment activities performed within the BfR Department of Food Safety, as well as in the hosting Unit Nutritional Risks, Allergies and Novel Foods. Furthermore, the fellow was supported by appropriate supervision to obtain experience in risk assessment of 'other substances' used in food supplements or fortified foods, with a focus on substances of plant origin ('botanicals', i.e. plant preparations and secondary plant compounds) and regular consultations in this regard with the supervisor as well as with other colleagues. At the BfR, the fellow participated in regular short seminars organised by the Department of Food Safety, with presentations on food safety-related (*in vitro* or *in vivo* experimental) ongoing research activities carried out at different units of the department. During the regular meetings of the host Unit of Nutritional Risks, Allergies and Novel Foods, the fellow presented the EU-FORA fellowship programme, as well as the intermediary results of her project on risk assessment of *A. muricata*. Moreover, the fellow was also given the opportunity to present and discuss the final results of her project within the EU-FORA programme at a departmental seminar on 7 July 2020.

Complementary to the 'learning by doing' placement at the BfR, a 3-week general induction training was arranged by EFSA in Parma (Italy) at the start of the Programme (September 2019), as well as other three specific training modules spread over the rest of the 12-month period.

In addition to the scheduled activities regarding the scientific project, the hosting institution, BfR, provided an additional training curriculum, and also enabled the fellow to participate in some other activities that played an important role in developing the general knowledge on risk assessment. For example, the fellow attended the 5th German Pharm-Tox Summit 2020 in March 2020 and presented results of her project as a conference poster on that occasion (Raclariu-Manolica et al., 2020). This also provided the opportunity for her to interact with a broad scientific community from academia as well as from regulatory institutions.

The following Table 1 provides an overview on the supporting activities organised or facilitated for the fellow by the BfR during the EU-FORA Fellowship.

Table 1: Supporting activities during the EU-FORA Fellowship

	Event title	Date, place	Note
Scientific meetings	One Health EJP Annual Scientific Meeting 2020	27–29 May 2020, Online	URL: www.ohejp2020.com
	5th German Pharm-Tox Summit 2020	2–5 March 2020, Leipzig University	URL: https://www.gpts-kongress.de/ Poster presentation: Risk assessment regarding the use of *Annona muricata* in food supplements (Abstract: Raclariu-Manolica et al., 2020)
Workshops/ Colloquium	Workshop 'Risk Assessment and Risk Management of Genetically Modified Organisms (GMO)'	9 June 2020, BfR, Berlin	Tutor: Hermann Broll
	Workshop 'Risk Assessment - Food contamination by plasticisers'	5 May 2020, BfR, Berlin	Tutors: Dr. Ralph Pirow, Dr. Sebastian Zellmer
	10th Berlin Workshop on Developmental Toxicology	19–20 February 2020, BfR, Conference center Berlin Biotechpark	URL: https://www.devtox.org/workshops_en.php
	Trust – how we understand, measure and build it	29 January 2020, BfR, Berlin	Speaker: Michelle Patel (Food Standards Agency, UK)

	Event title	Date, place	Note
	Creating characters for the BfR as a new line of communication	10 January 2020, BfR, Berlin	Speaker: Claudio Canales Rios
	Harmonized exchange of food safety models using web-based services from RAKIP and the AGINFRA + project	9 December 2019, BfR, Berlin	Tutors: Estibaliz Lopez de Abechuco Garrido, Esther Sundermann, Lars Valentin, Miguel de Alba Aparicio, Thomas Schüler, Tasja Buschhardt, Matthias Filter
	Big data and high-throughput-driven modeling of health effects of environmental agents	6 November 2019, BfR, Berlin	Speaker: Prof. Roland Grafström, Karolinska Institut, Stockholm, Sweden
Other activities	Nanopore Sequencing in Plants: From Greenhouse to Genome	18 February 2020, Webinar from Technology Networks	Speaker: Maximilian Schmidt
	An introduction to the BfR library and its services	15 November 2019, BfR, Berlin	Tutor: Mr. Benedikt Hummel, BfR library

3. Conclusions

3.1. Conclusions from *A. muricata* risk assessment

The results of the assessment show that substantial uncertainties exist regarding the safe use of *A. muricata*-based food supplements. The present data provide strong indications of neurotoxic potential of certain *A. muricata* preparations. However, the paucity of adequate studies, particularly related to long-term use of *A. muricata* supplements, currently does not allow the establishment of a safe intake level.

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

Participation in the EFSA EU-FORA work programme was a valuable opportunity for the fellow to obtain experience in risk assessment of herbal food supplements and other plant preparations. This was also an excellent opportunity for the fellow to consolidate her specialised knowledge and skills in food safety, particularly in herbal food supplements, by working according to European and international guidelines and standards. The general risk assessment methodology applied for this specific project is expected to be further extended and applied by the fellow to other substances with nutritional or physiological effected added to foods and food supplements.

Moreover, the EU-FORA programme provided a great environment to build a strong professional and personal network that will be used for future collaborations.

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Abbreviations

ACG	acetogenin
BfR	Bundesinstitut für Risikobewertung (German Federal Institute for Risk Assessment)
EEA	European Economic Area

EU-FORA	European Union Food Risk Assessment
i.v.	intravenous
RA	risk assessment
WHO	World Health Organization