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Risk assessment of substances used in food supplements: the example of the botanical *Gymnema sylvestre*

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Abstract

Botanicals and preparations derived from these are among the substances frequently added to foods and food supplements, yet the safety of many botanicals has not been systematically assessed. In the context of the EU-FORA fellowship programme, the fellow performed an assessment on the safety of the botanical *Gymnema sylvestre*, in accordance with EFSA's guidance on the assessment of safety of botanicals. Although preparations of *G. sylvestre* are marketed as food supplements, they may appeal to people who are suffering from metabolic syndrome and/or diabetes mellitus. A scientific literature search was carried out using PubMed/MEDLINE and EMBASE electronic databases. Experience was gained by the fellow in systematic data extraction from scientific publications, structuring of the data and evaluating toxicological key parameters, outcomes of clinical significance, pharmacokinetic and pharmacodynamic interactions, uncertainties and methodological shortcomings of studies. Limited evidence from toxicological *in vivo* studies and human clinical studies suggested lack of relevant adverse effects of this botanical. However, human studies provided some indications that certain *Gymnema* extracts may enhance the glucose-lowering effects of certain antidiabetic drugs. Considering the uncertainties for the composition of different *Gymnema* preparations, potential herb–drug interactions and the indications of glucose lowering or hypoglycaemic effects, the use of *Gymnema*-based food supplements in combination with authorised antidiabetic drugs may be associated with risks. The procedures learned for the safety evaluation of *Gymnema* may be similarly applied by the fellow for the risk assessment of other substances with nutritional or physiological effect added to foods and food supplements. Furthermore, apart from learning by conducting exercises in risk assessment, the fellow was able to develop other skills (e.g. communication skills), diversify his competencies and expand his network of scientific connections for future collaborations in the field of nutritional risk assessment.

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Keywords: *Gymnema sylvestre*, botanical, food supplement, risk assessment

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1. Introduction

Directive 2002/46/EC and Regulation (EC) 1925/2006 regulate the addition to food supplements or foods of (a) vitamins and minerals; and (b) 'other substances with a nutritional or physiological effect' (Directive 2002/46/EC) or 'other substances' (Regulation (EC) 1925/2006), respectively. Currently, the European Union (EU) legislation only lays down which vitamins and minerals may be added to food supplements or foods and which vitamin/mineral substances may be used; daily maximum amounts for vitamins and minerals have not been established. For 'other substances with a nutritional or physiological effect' or 'other substances', there are currently no specific provisions as to the substances (with the exception of two substances) which may be used in food supplements or foods. In addition, there are no provisions for daily maximum amounts in single products (food supplements or fortified foods) for individual substances.

Substances with nutritional or physiological effects that are frequently added to foods and food supplements include, among others, amino acids, essential fatty acids or certain botanicals or preparations derived from these. Food supplements and fortified foods containing botanicals have gained a substantial and constantly growing market share across Europe (Restani et al., 2018). The reasons for their increasing availability and use by consumers are complex, but the assumption that 'natural' can be equated with 'safe' is deemed to be a major factor. Nevertheless, herbs and/or herbal extracts may contain active ingredients that might be associated with harmful health effects. Examples of botanicals that have been shown or suspected to pose risks to human health include 'Ephedra herb and its preparations originating from *Ephedra* species', which are now prohibited in foods according to Commission Regulation (EU) 2015/403 (Part A, Annex III of the Regulation (EC) No 1925/2006) and 'Yohimbe bark and its preparations originating from Yohimbe (*Pausinystalia yohimbe* (K. Schum) Pierre ex Beille)', which has been placed under European Union scrutiny, pending a decision on whether or not to allow the use of the substance in foods (Part C, Annex III of the Regulation (EC) No 1925/2006). In many cases, safety aspects of botanicals used in food supplements for human health have been insufficiently evaluated and have not been covered adequately.

The plant *Gymnema sylvestre* and botanical preparations from these have had a long tradition of use, mainly in the Ayurvedic system of medicine, for a range of health ailments. While *Gymnema* has been primarily used with the intention of lowering raised blood glucose levels and ameliorating other co-morbid metabolic disorders such as dyslipidaemia, it has also been claimed to exhibit a wide range of other therapeutic effects, most of which lack sufficient scientific evidence (among others, antiarthritic, immunostimulatory, antimicrobial, hepatoprotective or anticancer effects) (Tiwari et al., 2014). *Gymnema* preparations have not been approved as drugs in Europe but are marketed as ingredients of certain food supplements, either alone or in combination with other herbs and/or micronutrients. On account of its use in the Ayurvedic system of medicine as an anticipated remedy for diabetes, food supplements containing *Gymnema* preparations may appeal to people who display one or more symptoms of metabolic syndrome. As a food supplement, it is used without medical supervision but it is conceivable that *Gymnema*-based food supplements may also be consumed instead of or in combination with antidiabetic drugs.

The risk assessment of *G. sylvestre* and preparations from these was performed in the context of the EFSA EU-FORA fellowship programme. This programme offers motivated professionals from EU national risk assessment authorities or other Article 36 organisations the opportunity to increase their knowledge and experience in food safety risk assessment (Bronzwaer et al., 2016). The aim of this programme is to contribute towards expanding the EU's community of scientists working in the field of risk assessment and at the same time enhance cooperation among Europe's food safety agencies as well as between them and EFSA. The fellow, whose home institution is the Hellenic Food Authority (EFET), Nutrition Policy and Research Directorate, was hosted by the German Federal Institute for Risk Assessment (BfR), Department of Food Safety, Unit of Nutritional Risks, Novel Foods and Allergies. The task assigned to the EU-FORA fellow was the preparation of a monograph for the risk assessment for *G. sylvestre* and preparations from these, under the guidance of unit members.

2. Description of work programme

2.1. Aims

The primary aim of the work programme was to become acquainted with the general aspects of risk assessment and risk communication as well as to gain experience specifically in the risk

assessment of botanicals (i.e. *G. sylvestri*) and other substances used in food supplements and fortified foods. The general methodology applied for the risk assessment of the chosen botanical should be suitable for application by the fellow also for the risk assessment of other substances with nutritional or physiological effect added to foods and food supplements. A further aim of the programme was to build professional connections with other colleagues in nutritional risk assessment (Bronzwaer et al., 2016), which can be expected to provide a supportive resource long after the completion of the fellowship, through exchange of views or common projects between the fellow's hosting site and the fellow's home institute.

2.2. Activities/methods

2.2.1. Preparation of a monograph for the risk assessment of *Gymnema sylvestri*

The selection of the botanical *G. sylvestri* was discussed with members of the BfR, also considering suggestions for botanicals that are currently being marketed as food supplements and for which a detailed safety assessment was deemed to be of importance. To avoid duplicating existing work, a prerequisite for the selection of this botanical was that its safety had not been previously evaluated by scientific bodies, international organisations (such as EFSA or the European Medicines Agency) or national authorities (such as BfR or the EFET). In the EFSA Compendium of Botanicals (EFSA, 2012), *G. sylvestri* (leaves) was listed in Annex A ('insufficient information' list), which includes botanicals appearing on a negative list or subject to restricted use in at least one European Member State but for which not enough information on possible substances of concern or adverse effects could be found, or for which the information present could not be verified. It is worth mentioning that this compendium does not address possible interactions between botanical substances or other products (e.g. allopathic medication) that would need to be taken into account when assessing safety, as described in the EFSA Guidance for the safety assessment of botanicals and botanical preparations (EFSA, 2012). Therefore, *Gymnema* preparations were selected as an example for risk assessment of substances used in food supplements. If *Gymnema* preparations are to be considered as a novel food or may be classified as pharmaceuticals was not addressed. (Such questions lie within the remit of the relevant authorities.)

The methodology that was followed for the preparation of the monograph of the *Gymnema*/*Gymnema* preparations was in accordance with the EFSA *Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements* (EFSA Scientific Committee, 2009). As specified in the EFSA Guidance, the scope of the present risk assessment does not address hazards linked to the presence of contaminants and food-borne pathogens in the botanical and the preparations from these.

Electronic literature searches were conducted to identify relevant scientific articles on *G. sylvestri*. Two of the most important scientific databases of references and abstracts on life sciences and biomedical topics, PubMed/MEDLINE and EMBASE, were systematically searched. Additional information from relevant webpages from Health Agencies/Bodies was sought as well as references from identified review articles. No restrictions on language or time of publication were imposed. Special attention was paid to identify and include in the assessment relevant scientific articles with common indigenous names as well as synonyms of the botanical. When common indigenous names (e.g. gurmar) were used in the search engine, special attention was paid that the correct species was identified.

A tiered approach was used for the identification of relevant scientific articles. An initial screening was conducted of the article titles identified via the two electronic scientific databases. Following this, the abstracts of potentially relevant articles were scrutinised. The complete manuscripts of the articles that appeared useful and necessary for the risk assessment of the botanical were retrieved for further detailed and thorough evaluation. The studies that were identified as relevant included: (a) those on chemical composition of the botanical/botanical preparations, the nature of extracts and bioavailability of their active constituents; (b) human intervention studies in healthy subjects as well as in people with disease; (c) acute, subchronic and chronic toxicological animal studies as well as animal studies investigating specific health effects of oral *Gymnema* administration; and (d) studies on potential pharmacokinetic and pharmacodynamic interactions between the botanical and allopathic drugs (especially antidiabetic drugs). Limited *in vitro* studies were also retrieved to understand better possible mechanisms related to health or safety aspects. Systematic reviews were also used to identify other scientific articles that were not included in the electronic databases used.

All identified human intervention studies on *G. sylvestre* were retrieved and evaluated. For safety aspects, human studies can be categorised in one of the three types: (1) studies in which no information is given for the occurrence or absence of adverse effects; (2) studies that report only the absence of adverse effects, without providing any further details; and (3) studies containing more detailed information on the occurrence of adverse effects in verum and control groups. For risk assessment purposes, studies that do not report on the occurrence or absence of adverse effects cannot be taken as proof that no adverse events occurred.

To facilitate systematic data extraction from scientific publications and the structuring of scientific data, tables were drawn for the selected human and animal studies. The tables contained information for the population groups (number of enrolled subjects, health status and concomitant use of antidiabetic medication), the type of *Gymnema* preparation (parts of the herb used, nature of extract and any other information for the standardisation of the extract), daily dosage, duration of the intervention, as well as safety laboratory parameters, clinical outcomes and information on absence/occurrence of adverse effects.

The focus was laid primarily on studies examining the effects of preparations of *G. sylvestre* alone, in healthy humans, as food supplements are intended mainly to complement one's diet and not to treat or cure diseases. However, *G. sylvestre* is marketed as a supplement that is purported to favourably affect blood glucose levels. As such, human intervention studies in which *Gymnema* preparations were administered to those suffering from glucose intolerance and diabetes mellitus (both insulin dependent and non-insulin dependent), with or without concomitant administration of antidiabetic drugs, were also evaluated for the safety of the preparations (e.g. Baskaran et al., 1990; Shanmugasundaram et al., 1990b; Al-Romaiyan et al., 2010; Zuniga et al., 2017). Furthermore, studies on the effects of formulas containing *G. sylvestre* in combination with other herbs and/or micronutrients were also studied for potential toxicity (e.g. Kurian et al., 2014; Mahajan et al., 2015). Information on sensitive population groups such as children, pregnant/lactating women, etc., was sought separately.

Randomised, double-blinded, placebo-controlled human intervention studies employing a sufficient number of participants that investigate not only the efficacy of the preparation but also potential toxic effects are usually the first line of choice. Due to the lack of these types of studies in the scientific literature for *G. sylvestre*, all human intervention studies were considered carefully for relevant information that might be used for the risk assessment of this botanical and preparations from these, including non-blinded studies and/or studies without control groups. Case reports of adverse effects were also considered. However, caution is to be exercised when interpreting such case studies for any conclusion on potential causality. For example, a published case report of liver toxicity related to the consumption of a *Gymnema* tea (Shiyovich et al., 2010) could point to potential adulteration or contamination of the tea with hepatotoxic substances or to a hepatotoxic potential of certain *G. sylvestre* constituents. However, in the light of preliminary evidence from animal studies, rather potential hepatoprotective effects of *Gymnema* preparations were observed (Srividya et al., 2010).

For the animal studies, emphasis was placed primarily on 'classical' toxicological studies (single dose or repeated dose toxicity studies) (Ogawa et al., 2004). However, animal studies that were carried out to assess the efficacy of the herb on various clinical, biochemical and laboratory parameters were also examined to obtain any useful information for potential safety issues (e.g. Shanmugasundaram et al., 1990a; Chattopadhyay, 1999; Shigematsu et al., 2001; Yadav et al., 2010).

Based on indications from both animal and human studies for potential interactions of *G. sylvestre* preparations with allopathic drugs (especially antidiabetic drugs), specific attention was paid to *in vitro* and *in vivo* studies that investigated primarily pharmacodynamic and/or pharmacokinetic interactions. For pharmacodynamic interactions, concomitant administration of the test substance has effects on targets such as receptors, enzymes, transcription factors, etc., leading to synergistic, additive or antagonistic effects with respect to the therapeutic effects, without altering the drug's concentration in the body. In pharmacokinetic interactions, co-administered test substance enhances or interferes with the absorption, distribution, metabolism or excretion of the conventional drug(s), resulting in changes in drug concentration in the body (e.g. Kamble et al., 2016).

It is known that pharmacokinetic interactions often involve inhibition or induction of the cytochrome P450 (CYP450) family of xenobiotic-metabolising enzymes. Enzyme inhibitors decrease enzyme activity, leading to increased concentrations of substrates (i.e. drugs being metabolised by enzyme system) and so, predisposing to drug toxicity. Enzyme inducers, conversely, increase the number of enzymes, leading to decreased concentrations of substrates, and have the potential to decrease the effectiveness of the drug.

In conclusion, the focus of the present project was to assess the possible risks and critical health aspects for the use of *G. sylvestre* in dietary supplements. The intention of this exercise was also to explore whether the derivation of health-based values that might form the basis of recommendations on *Gymnema* consumption would be possible and, in addition, to evaluate the uncertainties for this risk assessment.

2.2.2. Other activities during the EU-FORA fellowship

At the hosting site (BfR), the fellow participated in:

- a one-day seminar on literature search given by a staff member of the BfR. During the seminar, the fellow became acquainted with the electronic scientific databases that the BfR has access to and how to retrieve scientific articles.
- a two-day seminar on improving presentation skills 'Effective presentations'. The seminar focused on techniques for structuring a presentation and presenting facts and figures, ways to establish contact with the audience and finally ways to conclude a presentation.
- a seminar on risk assessment of foods containing genetically modified organisms.
- regular meetings of the Unit of Nutritional Risks, Allergies and Novel Foods of the BfR (which were held in English). These meetings offered the opportunity to the fellow to have fruitful and interesting discussions on the activities of other members of the Unit as well as on current nutrition-related risk assessment issues, e.g. for micronutrient supplementation or food fortification.
- short seminars (20 min each) organised regularly by the Department of Food Safety of BfR on the current scientific work carried out at different units of the BfR.

Additional activities:

- Presentation of the EU-FORA fellowship programme during a pre-Christmas one-day event at the BfR.
- Participation in international events organised by the International Affairs team of the BfR. These events provided the possibility for networking with other colleagues not only from Germany but also from around the world.
- Presentation of the project on *G. sylvestre* at the seminar of the Department of Food Safety of the BfR.
- Preparation of a poster for the EFSA conference on 'Science, Food, Society' in Parma on the 18–21st September 2018.

3. Conclusions

3.1. Conclusions for the assessment of the botanical

The safety assessment of *G. sylvestre* was complicated by a number of aspects.

In particular, the lack of standardisation in and comparability of *G. sylvestre* preparations posed a problem. The plant *G. sylvestre* may have different chemical composition, depending on geographical area (Pandey and Yadav, 2010) and growing conditions. For *Gymnema* preparations, different parts of the plant (leaves, stem and flowers) may be used which have different concentrations of active constituents. Furthermore, different modes of producing the preparation, including procedures involving different methods of extraction, may be used, resulting in very different composition and content of phytochemicals (Yadav et al., 2010). Certain *Gymnema* preparations that have been used in studies or in products found on the market have been reported to be standardised based on varying percentages of 'gymnemic acid', which is in itself a mixture of different compounds (Zarrelli et al., 2014).

Animal and human studies published in scientific journals have used a wide range of different *Gymnema* preparations. Therefore, extrapolating from one preparation to another with different chemical composition would not be possible, particularly as gymnemic acid (which is purported to be the active 'substance') is actually a mixture of compounds, some of which have not yet been characterised. Based on the resulting difficulties in performing a quantitative risk assessment, the available data were not regarded as being sufficient for the derivation of health-based guidance values.

The assessment of the botanical *G. sylvestre* was also challenging also to the insufficient number of studies containing relevant data for the safety assessment, the poor methodological approaches or poor study design, the lack of systematic data on dose and effect relationship and poor reporting or presentation of the outcomes in the scientific publications. Along these lines, it appears possible that unwanted or adverse effects resulting from the use of certain botanical preparations may be underreported (Bakhiya et al., 2017).

There are limited toxicological data from animal studies most of which were not adequately described or meeting the requirements of existing guidelines (e.g. the Organisation for Economic Co-operation and Development (OECD) test guidelines). Only with one type of *Gymnema* preparation (i.e. aqueous extract) a 'classical' subchronic or chronic toxicological study could be identified (Ogawa et al., 2004) (article only available in Japanese language). In this study, 0, 100, 1,000 or 10,000 mg of a *Gymnema* extract/kg feed were administered and no relevant adverse effects were observed. The authors identified a no-observed-effect level (NOAEL) 10,000 mg/kg feed per day (highest dose investigated), corresponding to 504 mg/kg body weight (bw) per day for male and 563 mg/kg bw per day for female rats. A slight but statistically significant increase in the relative weight of ovaries in all dose groups of female rats treated with the *Gymnema* extract deserves further clarification. It should also be pointed out that long-term repeated dose toxicity studies have not been performed with other types of extract such as ethanol extracts (used in some human clinical studies) or with higher doses.

A few other available experimental animal studies assessed the efficacy of different *Gymnema* preparations on plasma glucose and lipid parameters. In these studies, no adverse effects on liver, kidney or other organs were reported, when safety laboratory parameters were investigated.

No animal or human study could be identified for the effects of *G. sylvestre* alone on fertility and gestation.

The available data from a small number of human studies in healthy individuals do not point to any serious adverse effects following consumption of *G. sylvestre*. While a significant blood glucose lowering effect was observed after 10 days with administration of 2 g of dry leaf powder per day (Shanmugasundaram et al., 1981) and 6 g/day of an aqueous decoction of shade-dried powdered leaves (Khare et al., 1983) to a small number of individuals, no hypoglycaemic episodes were reported.

However, studies that investigated the efficacy of a water-soluble ethanol extract of *G. sylvestre* (GS4) at a dose of 400 mg/day in insulin-dependent diabetic patients (Shanmugasundaram et al., 1990b) and in non-insulin-dependent diabetic patients on antidiabetic drugs (Baskaran et al., 1990), reported the occurrence of hypoglycaemic episodes and adjustment of the drug regime. For example in the latter study by Baskaran et al. (1990), several weeks after *Gymnema* supplementation, virtually all patients developed secondary hypoglycaemic symptoms and the dose of drugs was reduced or discontinued (23% discontinued their conventional drug therapy). This serves as an indication of the possibility of herb–drug interactions. In addition, animal studies have suggested the risk of hypoglycaemia when *G. sylvestre* is taken concomitantly with antidiabetic drugs, pointing to potential pharmacodynamic interactions (Kamble et al., 2016) or tissue regeneration mechanisms (as presumed by Shanmugasundaram et al., 1990a for the specific animal model that was employed). Animal studies have provided some indications for potential pharmacokinetic interactions of *Gymnema* preparations with allopathic drugs (e.g. Vaghela et al., 2017), so suggesting possible interactions with CYP450 enzymes.

In conclusion, there are presently considerable knowledge gaps for the risk assessment of *G. sylvestre* preparations and open questions for whether results obtained with one preparation can be extrapolated to another *Gymnema* preparation. Also based on the lack of systematic data on dose and effect relationships, the available information was regarded as not being sufficient for the derivation of health-based guidance values for *Gymnema* or *Gymnema* preparations. Considering the uncertainties for the composition of different *Gymnema* preparations, potential herb–drug interactions and the concerns about glucose lowering or hypoglycaemic effects, the use of *Gymnema*-based food supplements in combination with (or as a substitute for) authorised antidiabetic drugs may be associated with risks when used without medical supervision.

3.2. Conclusions for the benefits gained from the fellowship

The fellow gained experience in systematic data extraction in a time-efficient manner from scientific publications and in the evaluation of toxicological and toxicokinetic studies. The general procedure for the safety evaluation of *Gymnema* can be followed by the fellow for the risk assessment of other

substances with nutritional or physiological effect added to foods and food supplements. No exposure assessment was performed due to the lack of available dietary intake data in the scientific literature.

The fellow realised the importance of not relying solely and automatically on the information presented in the abstract and/or the discussion/conclusions made by the authors but of the need to carefully analyse the data presented in the results section (Tables and Figures). A deeper insight of the presented data can certainly help any assessor decide whether the data are according to the authors' conclusion or to which extent an individual study might contribute to the overall weight of evidence. Various exercises were given to the fellow to establish an understanding of the importance of evaluating the presented data (ranging from biochemical and toxicological parameters to clinical outcomes) from individual articles that helped him to realise that, on some occasions, a different understanding of the presented data may explain the different conclusions made by different scientists for the risk assessment of the same substance.

The EU-FORA programme has provided a unique opportunity for the fellow to interact with experts in the field of nutritional risk assessment, obtain valuable experience and improve skills in performing nutritional risk assessment. The experience gained at the BfR may also lead to international collaboration opportunities well beyond the fellowship time.

While many nutritionists tend to focus primarily on diet/nutrient efficacy aspects, safety issues and potential adverse effects of nutrients and substances in foods and food supplements are often not of primary interest and hence, not adequately considered. To develop food-based dietary guidelines, one ought to be skilled in assessing not only the benefits but also the potential risks associated with consumption/over-consumption of certain foods, dietary supplements or individual substances added to supplements or fortified foods, in a systematic and time-efficient way. Therefore, early-to-middle career nutritionists (particularly those in the area of public health) and nutrition toxicologists who are interested in visiting an institution abroad for experience in nutrition risk assessment are greatly encouraged to look into and apply to the EU-FORA programme. Such programmes can greatly stimulate the fellow to think and work in a different framework and with a different mind-set, allow the fellow to diversify his/her competence and at the same time provide considerable opportunities for networking.

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Abbreviations

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| BfR | Bundesinstitut für Risikobewertung |
| bw | body weight |
| CYP450 | cytochrome P450 |
| EFET | Hellenic Food Authority |
| EU-FORA | The European Food Risk Assessment Fellowship Programme |
| NOAEL | no observed adverse effect level |
| OECD | Organisation for Economic Co-operation and Development |