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Risk assessment of white willow (*Salix alba*) in food

German Federal Institute for Risk Assessment (BfR),
Unit of Food Toxicology, Germany
Ewa Matyjasczyk and Regina Schumann

Abstract

This Technical Report contains a description of the activities within the work programme of the EU-FORA Fellowship on the risk assessment of white willow in food. The bark of different varieties of willow has had a long history of medical use as a means to reduce fever and as a painkiller. Willow bark is also used in weight loss and sports performance food supplements. The labelling of these products usually does not mention any restrictions to the length of use. The recommended doses for foods differ, sometimes exceeding doses recommended for pharmaceuticals. A systematic literature review on adverse effects potentially resulting from oral exposure to white willow (*Salix alba*) was performed. The aim of the study was to assess the risk for humans when consuming white willow bark in food. The preliminary results show that despite the long history of use only very limited data on toxicity of white willow bark are available. However, anaphylactic reactions in people with a history of allergy to salicylates may occur. Some other adverse effects of salicylates are considered to be of low relevance for the long-time consumption of white willow bark, mainly due to relatively low concentrations of salicin and the presence of compounds with gastroprotective action. However, it seems that the content of heavy metals, mainly cadmium, should be further addressed in risk assessment of white willow bark in food.

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Keywords: *Salix alba*, cortex, White willow, bark, risk assessment, food, food supplements

Correspondence: eu-fora@efsa.europa.eu

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1. Introduction

This Technical Report focuses on the steps of work performed within the European Food Safety Authority (EFSA) funded European Food Risk Assessment Fellowship Programme (EU-FORA) Fellowship. It contains the description of activities that composed the programme of work in the German Federal Institute for Risk Assessment (BfR). The work programme entitled 'Risk assessment of plant and plant preparations in food' had foreseen the risk assessment of 1 of the 11 proposed plants: *Hypericum perforatum*, *Salix alba*, *Rubus suavissimus*, *Phyllanthus emblica*, *Panax ginseng*, *Uncaria tomentosa*, *Muira puama*, *Echinacea purpurea*, *Harpagophytum procumbens*, *Boswellia serrata* and *Eleutherococcus senticosus*.

EU-FORA is a practical ('training by doing') programme that aims to increase the expertise and capacity available to risk assessment bodies at both European and national levels. It is aimed specifically at early- to mid-career scientists working in food safety organisations across Europe. (Bronzwaer et al., 2016).

2. Description of work programme

2.1. Aims

It was the aim of the project to provide a detailed insight into a broad range of prepared methods to assess the safety of plants/plant preparations using a science-based approach. By stepwise walking through the entire process of modern risk assessment, the EFSA Grant fellow had the chance to extend the knowledge on how to draft a risk assessment of 'botanicals' at all stages of the approach including hazard identification, hazard characterisation, exposure assessment and risk characterisation according to international guidelines and standards. The assessment of putative health risks also comprised deviation and discussion of risk-preventing options based on the available data. Finally, there was the chance to get insight into modern risk communication measures as practised in BfR.

2.2. Choice of plant

The organisational issues needed some time and effort from the fellow, the supervisor and the international team that was very helpful in supporting the fellow's settlement in BfR. However, apart from organisational matters, the first task was to choose the plant to work on. There are quite a number of plants that are used in food and it would be a challenge to choose from among all of them. However, BfR Unit of Food Toxicology had presettled a list of plants from which to choose. The following plants were proposed for risk assessment: *H. perforatum* (known as St John's-wort), *S. alba* (white willow), *R. suavissimus* (Chinese blackberry), *P. emblica* (Indian gooseberry), *P. ginseng* (Asian ginseng), *U. tomentosa* (cat's claw), *M. puama* (potency wood), *E. purpurea* (purple coneflower), *H. procumbens* (devil's claw), *B. serrata* (Indian olibanum) and *E. senticosus* (Siberian ginseng).

The topic of risk assessment in plants used in food is very wide (Schumann et al., 2015; Bakhiya et al., 2017; Dusemund et al., 2017). Which plant to choose was a serious decision to make and the fellow used not only the supervisors' advice but also engaged an experienced colleague from the Unit of Food Toxicology in the process. The fellow was a food specialist by education, but for some time had been working in the area of plant protection. Therefore, a topic somehow connected to her regular job as a scientist in the Plant Protection Institute – National Research Institute in Poland was chosen. *S. alba* (white willow) was chosen for risk assessment. Apart from its use in medicine (Shara and Stohs, 2015) and as a food supplement, *Salix* bark is used in plant protection and is registered in the European Union (EU) as a basic substance (Marchand, 2015). *Salix* bark uses as a fungicide, having an eliciting action on the crop's self-defence mechanisms, are approved (Matyjaszczyk, 2018).

2.3. Identity and nature of the source material

A further step was the identification of the source material. It means that very precise defining the plant and the part of plant to work on was necessary.

The genus *Salix* is formed by around 400 species (Wikipedia). Most of them prefer moist soils and cold and temperate regions. Numerous species can be used and are used in medicine. 'Willow bark' is sometimes defined simply as the 'bark of *Salix* tree species' (Natural Medicines Comprehensive Database 2007). Willow bark constituents include flavonoids, tannins and salicylates. The active constituent of willow bark is thought to be salicin. In some publications, the type of willow the bark comes from is not even mentioned.

For risk assessment, it is not relevant if the source material is *S. alba* or some other species of big *Salix* family. It has been shown by numerous studies that the salicin, flavonoids and tannins content as well as that of other components in the *Salix* plant material depend on numerous factors (Sugier et al., 2013; Gawlik-Dziki et al., 2014). One of the factors is the species used (Mleczeek et al., 2009; Krauze-Baranowska et al., 2013). Therefore, during the study, it was necessary to make sure that the data analysed concerned *S. alba* and not some other *Salix* plant species. The botanical identity of the plant was therefore as follows:

Family: Salicaceae

Genus: *Salix* L.

Species: *Salix alba*

Even this approach may be not sufficiently detailed, as the literature mentions a number of subspecies of *S. alba* and sometimes different terms are used to name the same plant. Moreover, sometimes systematics is not quite clear. Therefore, a list of different terms was prepared to consider during the study of *S. alba*.

The literature most often mentions the following subspecies:

Salix alba L.; *Salix alba* var. *caerulea* (Sm.) Sm.; *Salix alba* subsp. *micans* (Andersson) Rech. f.; *Salix alba* var. *vitellina* (L.) Stokes.

However, other names are also used, although these are often mentioned as synonyms:

Salix alba var. *alba*; *Salix alba* var. *australia* Poljakov; *Salix alba* f. *caerulea* (Sm.) Wimm.; *Salix alba* f. *ovalis* Wimm.; *Salix alba* f. *sericea* Wimm.; *Salix alba* var. *subintegra* N. Chao; *Salix alba* subsp. *vitelina* (L.) Arcangeli; *Salix alba* f. *vitelina* (L.) Wimm.

Another point of identification of the source material was to name the plant part used for risk assessment. For *Salix* (and other trees as well), the part of the plant strongly influences the content of numerous components, and it is therefore crucial for risk assessment to be specific (Unterbrunner et al., 2007; Zarubova et al., 2015). The source material 'white willow bark' is not as simple as it sounds, as this describes more than just the bark. The definition in the Martindale reference very precisely describes the plant part used as a source material for medical products as 'the whole or fragmented dried bark of young branches or whole dried pieces of current year twigs' (Brayfield, 2017).

Some analysis performed for willow could not be considered for studies because their data gave values of certain compounds in wood, leaves or roots.

2.4. Manufacturing process

Manufacturing processes can obviously influence the content of components in the final product. However, for willow bark, the manufacturing process is not very sophisticated as very often simply powdered or comminuted herbal substance is used. Therefore, for white willow bark, the manufacturing process does not seem to influence the composition of the source material.

It is also possible to use dried hydroalcoholic or aqueous extracts, tinctures or fluid extracts (Schilcher and Kammer, 2003); however, the inclusion of powdered or comminuted herbal substances is the worst-case scenario for risk assessment.

2.5. Chemical composition

In the next step of the research project, a list of secondary plant ingredients was to be established, as well as predictions of their genotoxic/carcinogenic potency based on the literature review. Based on the results obtained, substances were to be selected for subsequent *in vitro* studies with long/short time exposure to the selected secondary plant ingredients (induction of steatosis, microarray analysis, reporter gene assays: promoter analysis CYP7A1, interaction and nuclear receptors).

It was therefore necessary to use the literature as well as literature databases to look for the required information. However, regarding the description of the composition, old-fashioned printed compendia proved to be far more useful than internet sources.

In some cases, the most recent and most reliable data on the composition of products are to be found online. However, for plant components (at least white willow components), the printed compendia were easy to find and the information in these was compact and comprehensive. Mining the internet for the same data would be much more time consuming and would require much more

criticism and double-checking of the sources used. Of course the fellow was very conveniently placed for such studies. BfR is a governmental body dealing, among others, with food safety, therefore, the fellow had access to the whole library, as well as the small collection library of the Unit of Food Toxicology at her disposal. In addition, she was able to obtain advice from supervisors as to which were the most reliable and comprehensive manuals to use. However, in the current digitalised world, maybe it is worth to point out, that at least in some cases using books is still a much easier way to find relevant data, than looking for data on the Web.

2.6. Toxicological data

After identifying the secondary plant ingredients, the next task was to predict their genotoxic and carcinogenic potency. Here, it was necessary to make use of internet literature databases. However, the databases most often used by the fellow when searching for literature on plant protection were not always the best for human toxicology data. Regarding the toxicological data, PubMed and EMBASE databases were the most useful to work with. BfR as a governmental institution has a large number of databases available, so again the fellow was in a convenient position and could use these interchangeably. However, for people working in less equipped institutions, it may be a good tip that sometimes, especially while approaching certain topics from different angles, to try other databases from the library of another university or governmental institution, which may have access to databases that better suit the topic.

The use of papers containing toxicological data was the most challenging part of the fellow's task so far. She had no toxicological background and the technical vocabulary proved to be difficult for her to understand. In spite of the supervisor's assistance, looking for toxicological data on *S. alba* was a lengthy process because it was very difficult to find relevant studies. The most helpful publication was from the European Medicines Agency (EMA, 2017). It in fact did not contain or quoted any sources that contained data on toxicity of *S. alba*, but at least it stated information that confirmed findings or rather the lack of findings: namely that such data for the main components of *S. alba* are basically non-existent.

It remained, however, one more path to follow regarding the risk assessment of *S. alba*. From the fellow's agricultural knowledge, she was aware that different species of *Salix* are used for phytoremediation and phytostabilisation or are used to clean up soil contaminated with hazardous compounds, particularly heavy metals (Kacalkova et al., 2015; Mayerova et al., 2017). Therefore, as *Salix* species are known for their 'remarkable capacity to concentrate toxic heavy metals' (Chen et al., 2013), it was interesting to check if there is a risk that bark consumed by humans may contain excessive toxic heavy metals. Indeed, this idea proved to be the case. Heavy metals are present in willow bark in significant amounts.

2.7. Exposure

It is pretty logical that exposure occurs by oral consumption. In assessing exposure to *S. alba* in food, there should be consideration of how much white willow bark humans consume.

Tree bark is not typical component of meals in Europe and, when discussing the topic, people were generally surprised that it is consumed in food at all. However, it is consumed as an ingredient of weight-loss supplements (Sharpe et al., 2006) as well as sports performance products (Shara and Stohs, 2015). Some food supplements contain white willow bark as one of numerous components, plus willow bark is sold for human consumption as a powder.

When performing the exposure study for *S. alba* in food, a useful hint was given by an experienced colleague from the Unit of Food Toxicology to assume that the highest consumption level was that recommended for medical products.

However, the fellow carried out her own market research by checking different online shops with food supplements and analysed the labels of the offered products. In some cases, it was challenging to get information from the labels due to poor quality of pictures and sometimes the labels were not very informative. However, spending some time on this task it appeared that for food supplements containing multiple components, the recommended dose of *S. alba* was indeed usually lower than for medical products. Recommendations for medical products could therefore be considered as the worst case scenario. However, in food supplements containing white willow bark as the only or as the main component, there were cases in which maximum recommended dose of willow bark in food was higher than the maximum dose recommended for medical products.

2.8. Safety assessment based on available knowledge

It was not possible to consider the toxicity of secondary plant ingredients, as full data are not available. However, regarding the content of the salicylic compounds, there seems to be consensus in the literature that willow bark has a broader mechanism of action and is devoid of serious adverse events in comparison with aspirin (Vlachojannis et al., 2014; Dragos et al., 2017).

To calculate safety based on available knowledge on heavy metals, the EFSA published statements on tolerable weekly intake were considered (EFSA CONTAM Panel, 2010, 2011) as well as the literature data on content of heavy metals in willow bark.

It was debatable what should be considered as a worst-case scenario of heavy metal content in willow bark. In many European countries, willows grow in semi-wild conditions in different places. They can be often spotted in rural areas or alongside roads and streams, and among fields or meadows. Sometimes, however, they grow in proximity to abandoned buildings and uninhabited places. It is therefore neither unusual nor surprising for a passer-by to spot willows in the proximity of an abandoned mine. However, grounds surrounding some old mines and smelting places may contain uncommonly high levels of heavy metals. Moreover, different species of willows are often purposefully planted in places contaminated with heavy metals for their phytoremediation properties. Bark coming from such willows may be heavily contaminated with heavy metals. Conversely, it may be assumed that willow bark that serves as a raw material for food or medical industry would be acquired from safe places. Therefore, for the worst-case scenario calculation, the fellow decided to use a scenario in which willow bark comes from areas that are known to be polluted with heavy metals, but that are used in agriculture.

2.9. EU-FORA Fellowship supporting programme

In addition to her work in Unit of Food Toxicology, participation in weekly seminars and consultations with the supervisor as well as with some other colleagues, during the period of EU-FORA Fellowship Programme the fellow benefited from other activities. The four training modules in Parma, Vienna, Berlin and Athens were very interesting and were common for all EU-FORA fellows as described in the 'EU-FORA Fellowship Programme year 2018–2019'.

However, the hosting institution, BfR, provided additional training curriculum, as well as enabling the fellow to participate in some other activities that developed her general knowledge as well as her knowledge on risk assessment. Table 1 presents the supporting activities organised or facilitated for the fellow by BfR during the EU-FORA Fellowship.

Table 1: Supporting activities organised or facilitated by the hosting institution, the German Federal Institute for Risk Assessment, during the EU-FORA Fellowship

	Title	Date
Training on risk assessment	Workshop 'Risk assessment of plasticisers'	22.11.2017
	Workshop 'What does the future hold for harmonised human health risk assessment of plant protection products?'	23–24.11.2017
	GMO Risk Assessment Workshop	22–23.5.2018
Other activities	Participation once a week in department seminars with presentations of food safety-related (<i>in vitro</i> or <i>in vivo</i> experimental) research activities	Every week
	Training 'Library Introduction – Databases and Organisation of Information in BfR'	29.9.2017
	Conference 'Efficacy and risks of biorational products in integrated pest management (IPM) strategies - acceptable?'	13–14.12.2017
	Training 'Effective Presentations'	20–21.2.2018
	Participation in International Events organised by International Affairs team with an aim to provide an opportunity for social and professional networking	Every quarter
	Visit in Department of Pesticides Safety	TBC
	Visit in Department of Safety in the Food Chain	TBC

3. Conclusions

The programme of the fellowship reached two aims:

- 1) Enabling the fellow to gain first-hand experience on risk assessment as well as extend the knowledge on how to elaborate risk assessment of 'botanicals' at all stages of the approach including hazard identification, hazard characterisation, exposure assessment and risk characterisation according to international guidelines and standards.
- 2) Performing risk assessment of white willow (*S. alba*) in food. Very limited data on toxicity of white willow bark are available. However, regarding the available data, the content of heavy metals, mainly cadmium, may be of concern regarding white willow bark in food.

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Abbreviations

BfR	German Federal Institute for Risk Assessment
EMA	European Medicines Agency
EU-FORA	The European Food Risk Assessment Fellowship Programme
GMO	genetically modified organism
IPM	integrated pest management