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Safety and efficacy of a feed additive consisting of a tincture derived from the roots of *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (taiga root tincture) for use in dogs, cats and horses (FEFANA asbl)

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Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of a tincture from the roots of *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (taiga root tincture) when used as a sensory additive in feed for dogs, cats and horses. The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) concluded that the additive is safe for dogs, cats and horses at the maximum proposed use level of 460.7, 489.5 and 140.7 mg/kg complete feed, respectively. The additive was considered safe for consumers when used at the proposed conditions of use in horses for meat production. The additive under assessment should be considered as irritant to skin and eyes, and as a skin and respiratory sensitiser. The use of the taiga root tincture as a flavour in feed for horses was not expected to pose a risk for the environment. Since the root of *E. senticosus* has flavouring properties and its function in feed would be essentially the same as that in food, no further demonstration of efficacy is considered necessary for the tincture under assessment.

Keywords: sensory additives, flavouring compounds, *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim., taiga root tincture, eleutheroside E, eleutheroside B, safety

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1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 4(1) of that Regulation lays down that any person seeking authorisation for a feed additive or for a new use of feed additive shall submit an application in accordance with Article 7. In addition, Article 10(2) of that Regulation specifies that for existing products within the meaning of Article 10(1), an application shall be submitted in accordance with Article 7, within a maximum of 7 years after the entry into force of this Regulation.

The European Commission received a request from Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)[2] for authorisation/re-evaluation of 29 preparations (namely dill herb oil, dill seed extract, dill tincture, dong quai tincture, celery seed oil, celery seed extract (oleoresin), celery tincture, hares ear tincture, caraway seed oil, caraway oleoresin/extract, coriander oil, cumin oil, taiga root extract (solvent-based, sb), taiga root tincture, fennel oil, fennel tincture, common ivy extract (sb), opoponax oil, ginseng tincture, parsley oil, parsley tincture, anise oil, anise tincture, ajowan oil, Ferula Assa-foetida oil, anise star oil, anise star tincture, anise star terpenes and omicha tincture) belonging to botanically defined group (BDG) 02 – *Apiales/ Austrobaileyales* when used as feed additives for all animal species (category: sensory additives; functional group: flavourings). During the assessment, the applicant withdrew the application for nine preparations (dill seed extract, celery seed extract (oleoresin), caraway oleoresin/extract, opoponax oil,[3] parsley oil, hares ear tincture, taiga root extract (sb), ajowan oil[4] and parsley tincture[5]) and requested a change in the species limiting the application for authorisation to dogs, cats and horses.[6] During the course of the assessment, this application was split and the present opinion covers only one out of the 20 remaining preparations under application: taiga root tincture from *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.[7] for dogs, cats and horses.

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 4(1) (authorisation of a feed additive or new use of a feed additive) and under Article 10(2) (re-evaluation of an authorised feed additive). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 24 June 2019.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of the feed additive consisting of a tincture from the roots of *E. senticosus* (taiga root tincture), when used under the proposed conditions of use (see Section 3.2.3).

The remaining 19 preparations belonging to botanically defined group (BDG) 02 – Apiales/ Austrobaileyales under application are assessed in separate opinions.

1.2. Additional information

Taiga root tincture from '*Eleutherococcus senticosus* Rupr. & Maxim. = *Acanthopanax senticosus* Harms.' is currently authorised as a feed additive according to the entry in the European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003 (2b natural products – botanically defined). It has not been assessed as a feed additive in the EU.

[1] Regulation (EC) No 1831/2003 of the European Parliament and of the council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.
[2] On 13/03/2013, EFSA was informed by the applicant that the applicant company changed to FEFANA asbl, Avenue Louise 130 A, Box 1, 1,050 Brussels, Belgium.
[3] On 27 February 2019, EFSA was informed by the applicant about the withdrawal of the applications on dill seed extract, celery seed extract (oleoresin), caraway oleoresin/extract, and opoponax oil.
[4] On 2 April 2020, EFSA was informed by the applicant about the withdrawal of the applications on parsley oil, hares ear tincture, taiga root extract (sb), ajowan oil.
[5] On 9 December 2020, the applicant informed EFSA about the withdrawal of the application on celery tincture.
[6] Technical dossier/Supplementary information August 2022/ SIn reply_taiga_root_tincture.
[7] Synonyms: *Acanthopanax senticosus* (Rupr. et Maxim.) Harms., *Hedera senticosa*.

There is no specific EU authorisation for any *E. senticosus* preparation when used to provide flavour in food.

The World Health Organization (WHO) issued a monograph on Radix Eleutherococci (WHO, 2002).

'Eleutherococcus (Eleutherococci radix)' is described in a monograph of the European Pharmacopoeia 10.0 (PhEur, 2020). It is defined as the dried, whole or cut underground organs of fragmented roots of *E. senticosus* (Rupr. & Maxim.) Maxim.

For human medicinal uses, the European Medicines Agency (EMA) issued an assessment report on *E. senticosus* (Rupr. & Maxim.) Maxim., radix (EMA, 2014a) and a community herbal monograph (EMA, 2014b).

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[8] in support of the authorisation request for the use of taiga root tincture as a feed additive.

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA or other expert bodies, peer-reviewed scientific papers, other scientific reports and experts' knowledge, to deliver the present output.

Several of the components of the tincture under assessment have been already evaluated by the FEEDAP Panel as chemically defined flavourings (CDGs). The applicant submitted a written agreement to reuse the data submitted for the assessment of chemically defined flavourings (dossiers, publications and unpublished reports) for the risk assessment of preparations belonging to BDG 2.[9]

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of the phytochemical markers in the additive. The evaluation report is related to the methods of analysis for each feed additive included in BDG 02 (Apiales and Austrobaileyales). During the assessment, the EURL issued a partial report,[10] and an addendum[11] which included the additive under assessment, taiga root tincture. In particular, for the characterisation of taiga root tincture the EURL recommended a method based on high-performance liquid chromatography coupled with ultraviolet detection (HPLC-UV) for the quantification of the phytochemical markers *Eleutheroside B* (sinapyl alcohol 4-*O*-glucoside) and *Eleutheroside E* (syringaresinol-di-*O*-glucoside) in taiga root tincture.[12]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of taiga root tincture is in line with the principles laid down in Regulation (EC) No 429/2008[13] and the relevant guidance documents: Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA SC, 2009), Compendium of botanicals that have been reported to contain toxic, addictive, psychotropic or other substances of concern (EFSA, 2012), Guidance for the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012a), Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012b), Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017a), Guidance on the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017c), Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018), Guidance document on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals

[8] FEED dossier reference: FAD-2010-0221.
[9] Technical dossier/Supplementary information/Letter dated 29/04/2021.
[10] Preparations included in the partial report: dill herb oil, dill tincture, dong quai tincture, cumin oil, fennel tincture, parsley tincture, anise tincture, star anise tincture and ferula assa-foetida oil.
[11] Preparations included in the addendum: celery seed oil, caraway seed oil, coriander oil, taiga root tincture, fennel oil, common ivy extract (sb), ginseng tincture, anise oil, anise star oil, anise star terpenes and omicha tincture.
[12] The full report is available on the EURL website: https://joint-research-centre.ec.europa.eu/publications/fad-2010-0221_en
[13] Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.

(EFSA SC, 2019a), Statement on the genotoxicity assessment of chemical mixtures (EFSA SC, 2019b), Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment (EFSA SC, 2019c).

3. Assessment

The additive under assessment, taiga root tincture, is obtained from the dried roots of *E. senticosus* (Rupr. & Maxim.) Maxim. It is intended for use as a sensory additive (functional group: flavouring compounds) in feed for dogs, cats and horses.

3.1. Origin and extraction

E. senticosus (Rupr. & Maxim.) Maxim. is a woody shrub native to the northern parts of Asia, belonging to the family Araliaceae. Reference to the use of its rhizome and roots, either in the form of a dry powder or as an extract, is found both in Russian and Chinese traditional medical systems as an alternative to ginseng. For this reason, it is often referred to as Siberian ginseng, although an alternative term 'eleuthero' has been introduced in an attempt to avoid confusion with true ginseng (*Panax* spp.). Extracts may also be described as 'taiga root extracts' which derives from the Russian word for the coniferous forests of Siberia, where *E. senticosus* forms a large part of the undergrowth.

The tincture is obtained by extraction of the dried rhizome and roots of *E. senticosus* using a water/ethanol mixture (75/25, v/v) for a period of 21 days under ambient conditions. The ratio of dry raw material to solvent is 1:5 (w/v). Following extraction, the tincture is obtained by pressing to remove solid material and clarified by filtration.

3.2. Characterisation

3.2.1. Characterisation of the tincture

The tincture under assessment has a density of 966–991 kg/m^3 (979 kg/m^3 on average, five batches).[14] By specification the product is a water/ethanol (75/25, v/v) solution, with a dry matter (DM) content of 0.5–1.5%, which contains 0.0001–0.005% (+)-syringaresinol-di-*O*-glucoside[15] (synonym: eleutheroside E) and 0.0001–0.005% sinapyl alcohol 4-*O*-glucoside (synonyms: eleutheroside B, syringin or syringoside).[6]

Table 1 summarises the results of the proximate analysis of five batches of the additive (of Chinese origin) expressed as % (w/w).[16] The solvent represents about 99% of the additive, and the DM content ranged between 0.70 and 1.05 g/100 mL (average 0.92 g/100 mL, when expressed as w/v).[17]

Table 1: Proximate analysis of taiga root tincture (*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.) based on the analysis of five batches (mean and range). The results are expressed as % (w/w)

Constituent	Mean[(a)]	Range
	% (w/w)	% (w/w)
Dry matter	0.95	0.71–1.07
Lipids	<0.3	<0.3
Protein	0.15	0.1–0.2
Fibre	<0.5	<0.5
Sugars	0.7	0.6–0.9
Ash	0.1	0.1
Solvent (water/ethanol, 75/25, v/v)	99.05	98.93–99.29

(a): Mean calculated on five batches.

[14] Technical dossier/Supplementary information August 2022/Annex_IV_Eleutherococcus_Gravitational Analysis_Dry Matter_Density.
[15] (+)-Syringaresinol-4,4-*O*-β-D-diglucoside.
[16] Technical dossier/Supplementary information September 2021/Annex_III_Angelica_Nutritional Analysis_Microbial_Dioxins and Annex_IV_Angelica_Gravitational Analysis_Dry Matter_Density.
[17] Technical dossier/Supplementary information September 2021/Annex_IV_Angelica_Gravitational Analysis_Dry Matter_Density.

The fraction of secondary metabolites was characterised in the same batches of the additive and the results are summarised in Table 2. Phenols determined by spectrophotometry (at λ 765 nm) are expressed as gallic acid equivalents.[18] Individual compounds were determined by HPLC with UV detector: phenolic compounds including lignans and coumarins (detected at 220 nm),[19] and non-phenolic organic acids (at 210 nm).[20] No essential oil constituents were identified by gas chromatography–mass spectrometry (GC–MS).[21] Analytical results are expressed as μg/mL.

Table 2: Characterisation of the fraction of secondary metabolites of taiga root tincture (*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.) based on the analysis of five batches (mean and range). The results are expressed as μg/mL of taiga root tincture

Constituent	CAS No	FLAVIS No	Mean	Range
			μg/mL	μg/mL
Phenols (total, by spectrophotometry)	–	–	285	237–336
Lignans (HPLC, 220 nm)				
(+)-Syringaresinol-di-*O*-glucoside (eleutheroside E, **1**)	39432-56-9	–	14.2	9.2–20
Syringaresinol	21453-69-0	–	5.6	2.7–10.6
Unknown lignans	–	–	29.7	8.7–55.9
Total lignans (HPLC)			49.4	28.9–86.5
Other phenolic compounds (HPLC, 220 nm)				
Sinapyl alcohol 4-*O*-glucoside (eleutheroside B, syringin, **2**)	118-34-3	–	10.6	8.3–13.7
Coniferyl alcohol	458-35-5	–	3.4	1.7–4.2
Sinapyl alcohol	537-33-7	–	0.6	0.3–1.0
Ferulic acid glucoside	7196-71-6	–	9.0	6.5–11.8
Protocatechuic acid (3,4-dihydroxybenzoic acid)	99-50-3	08.133	3.7	3.3–4.1
Syringic acid (4-hydroxy-3,5-dimethoxybenzoic acid)	530-57-4	08.087	2.4	1.8–3.1
Chlorogenic acid	327-97-9	–	10.0	8.4–12.2
3,5-Dicaffeoylquinic acid	89919-62-0	–	11.1	9.0–12.8
Vanillic acid (3-methoxy-4-hydroxybenzoic acid)	121-34-6	08.043	1.3	1.1–1.7
Caffeic acid (3,4-dihydroxybenzeneacrylic acid)	331-39-5	–	2.3	1.8–2.7
Ferulic acid (4-Hydroxy-3-methoxycinnamic acid)	1135-24-6	08.089	4.2	3.1–5.3
1,4-Dicaffeoylquinic acid	1182-34-9	–	5.1	2.9–8.4
Unknown phenolic compounds	–	–	12.9	7.9–18.6
Total phenolic compounds			76.8	61.8–91.2
Coumarins (HPLC, 220 nm)				
Isofraxidin (6,8-dimethoxy umbelliferone)	486-21-5	–	2.75	1.13–3.70
Isofraxidin-7-glucoside (eleutheroside B1, **3**)	483-91-0	–	3.67	2.21–5.25
Total coumarins			6.42	5.09–8.75
Non-phenolic organic acids (HPLC, 210 nm)				
Oxalic acid	110-17-8	08.025	182	123–247
Fumaric acid	144-62-7	–	4.9	2.4–7.3
Total non-phenolic organic acids	–	–	187	129–254
Total identified[(a)]			478	446–515

(a): Considering the sum of total phenols (by spectrophotometry), organic acids and coumarins.

The sum of identified secondary metabolites (478 μg/mL) accounts on average for 5.7% of the dry matter fraction of the tincture.

[18] Technical dossier/Supplementary information August 2022/Annex_V_Eleutherococcus_Total_Phenols.
[19] Technical dossier/Supplementary information September 2021/Annex_II_Angelica_HPLC_Analysis_Chlorog Ac._Ferul Ac.Coniferylferulate.
[20] Technical dossier/Supplementary information August 2022/Annex_VI_Eleutherococcus_HPLC_Organic Acids.
[21] Technical dossier/Supplementary information August 2022/Annex_VIII_Eleutherococcus_GC-MS_Essential oil.

The structures of the main secondary metabolites detected in taiga root tincture, namely (+)-syringaresinol-4,4′-*O*-β-D-diglucoside (eleutheroside E, **1**), syringin (eleutheroside B, **2**) and isofraxidin-7-*O*-glucoside (eleutheroside B_1, **3**), are shown in Fig. 1.

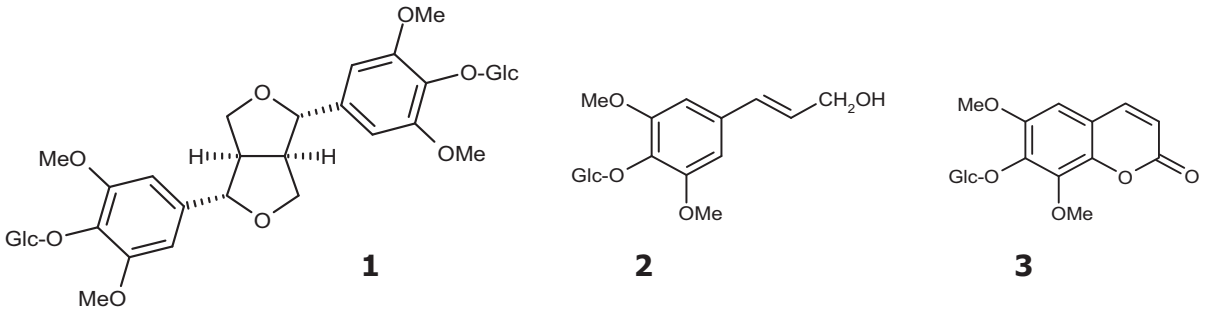

Figure 1: Structures of the main secondary metabolites identified in taiga root tincture: (+)-syringaresinol-4,4′-*O*-β-D-diglucoside (eleutheroside E, **1**), syringin (eleutheroside B, **2**) and isofraxidin-7-*O*-glucoside (eleutheroside B_1, **3**).

The applicant made a literature search for the chemical composition of *E. senticosus* and its preparations and the identity of any recognised substances of concern.[22] The Commentary on the European Pharmacopeia (Commentary on the PhEur, 2019) reports on the occurrence of **lignans** ((+)-syringaresinol-4,4′-*O*-β-D-diglucoside (eleutheroside E), (−)-sesamin (eleutheroside B_4), (+) and (−)-syringaresinol, (−)-syringaresinol-4-*O*-β-D-glucoside (eleutheroside E_1), (+)-syringaresinol-*O*-β-D-glucoside and (−)-syringaresinol-4,2′-*O*-β-diglucoside (acanthosid D)), **phenylpropane derivatives** (syringin (eleutheroside B)), **coumarins** (isofraxidin, isofraxidin-7-*O*-glucoside (eleutheroside B_1), 4-*O*-ethylumbelliferone), **steroids** (daucosterol (β-sitosterol-3-*O*-β-D-glucoside, eleutheroside A)), **triterpene saponins** (glycosides of oleanolic acid (eleutherosides I, K, L, M)), **polysaccharides** and some **essential oil** in the underground organs of *E. senticosus*. This is in agreement with the compositional data reported in the WHO monograph (WHO, 2002) and the EMA report (EMA, 2014a).

Two hydroxycoumarins (isofraxidin and isofraxidin-7-glucoside (eleutheroside B_1)) were detected in taiga root tincture in trace concentrations (on average, 2.75 and 3.67 μg/L, see Table 2) and together accounted for < 0.08% of the DM fraction. 4-*O*-Ethylumbelliferone and triterpene saponins were not detected in the tincture.

3.2.1.1. Impurities

Data on impurities were provided for three batches of taiga root tincture. Mercury was below the corresponding limit of quantification (LOQ, 0.002 mg/kg) in all batches. Arsenic was below the LOQ (< 0.005 mg/kg) in two batches and was 0.0081 mg/kg in one batch. Cadmium was below the LOQ in one batch (< 0.0004 mg/kg) and ranged between 0.0007 and 0.0008 mg/kg in the other batches. The concentrations of lead were in the range 0.0038–0.0044 mg/kg. In the three batches, mycotoxins were below the corresponding LOQ and pesticides were not detected in a multiresidue analysis, with a few exceptions (diethyltoluamide (DEET) 0.10–0.13 mg/L, ethylbutylacetylaminopropionate 0.014 mg/kg in one batch and piperonylbutoxide was < 0.01 mg/kg).[23] Polychlorinated dibenzo-*p*-dioxin (PCDD) and polychlorinated dibenzofuran (PCDF) were below the corresponding LOQ. The calculated upper bond for the sum of dioxins was 31.6 ng WHO PCDD/F-TEQ (World Health Organisation polychlorinated dibenzo-*p*-dioxin (PCDD) and polychlorinated dibenzofuran (PCDF) toxic equivalents (TEQ))/kg, the sum of dioxin and dioxin like PCBs was 33 ng WHO PCCD/F + PCB TEQ/kg.[24]

[22] Technical dossier/Supplementary information August 2022/ Literature search_taiga_root_tincture.

[23] Technical dossier/Supplementary information August 2022/Annex_VIII_Eleutherococcus_Heavy Metals, Mycotoxins, Pesticides. LOQ for heavy metals and arsenic: < 0.005 mg/kg for arsenic, < 0.002 mg/kg for mercury and < 0.0004 mg/kg for cadmium; LOQ for individual pesticides: 0.001–0.005 mg/L; LOQ for mycotoxins: < 0.1 μg/kg for aflatoxins B1, B2, G1 and G2, < 1 μg/kg for ochratoxin A, < 2 μg/kg for zearalenone, α- and β-zearalenone, HT2-toxin, T2-toxin cytrochalasin E and sterigmatocystin, < 5 μg/kg for nivalenol, fusarenon X and diacetoxyscirpenol, and < 10 for deoxynivalenol, deoxynivalenol-3-glycoside, 3-acetyldeoxynivalenol, 15-acetyldeoxynivalenol, citrinin, patulin and fumonisins B1, B2 and B3.

[24] Technical dossier/Supplementary information August 2022/Annex_III_Eleutherococcus_Nutritional Analysis_Microbial_Dioxins.

Analysis of microbial contamination of five batches of taiga root tincture indicated that *Salmonella* spp. were absent in 25 g, and *E. coli* and *Enterobacteriaceae* were < 1 and < 0.1 colony forming unit (CFU)/g, respectively.[22]

The detected amounts of the undesirable substances do not raise safety concerns.

3.2.2. Shelf life

The applicant states that the typical shelf life of flavourings is at least 12 months, when stored in tightly closed containers under standard conditions. However, no data supporting this statement were provided.

3.2.3. Conditions of use

Taiga root tincture is intended for use in complete feed for dogs, cats and horses, at a maximum use level of 0.12, 0.03 and 1.15 mL/head per day, respectively, corresponding to 460.7, 489.5 and 140.7 mg/kg complete feed.

3.3. Safety

The safety assessment of the additive is based on the highest proposed use levels (see Section 3.2.3).

No studies to support the safety for target animals, consumers and users were performed with the additive under assessment. The applicant provided a literature search on the absorption, distribution, metabolism and excretion (ADME) and on the toxicology of preparations obtained from *E. senticosus*.[25]

The additive under assessment, taiga root tincture, on average consists of about 99% (w/w) water/ethanol mixture. The concentration of plant-derived compounds is about 1% (w/w) of the tincture. The dry matter included minerals (expressed as ash), protein, lipids and carbohydrates, which are not of concern and are not further considered.

Among the identified secondary plant metabolites (see Table 2), up to 0.009% (w/w) of the tincture is constituted by simple phenols (12 compounds were identified), 0.009% (w/w) by lignans (two compounds identified), 0.07% (w/w) by hydroxycoumarins (isofraxidin and isofraxidin-7-glucoside) and 0.026% (w/w) by non-phenolic organic acids (oxalic and fumaric acids).

Simple phenols and non-phenolic organic acids, including oxalic acid and fumaric acid, will be readily metabolised and excreted and are not expected to accumulate in animal tissues and products. They also do not raise concern for genotoxicity. These compounds are not of concern at concentrations resulting from the use of the additive at the maximum proposed use level in feed and are not further considered in the assessment.

The next sections will mainly focus on lignans and hydroxycoumarins, based on the information provided by the applicant in the form of literature searches and Quantitative Structure–Activity Relationship (QSAR) analysis.

3.3.1. Absorption, distribution, metabolism and excretion of lignans and hydroxycoumarins

No ADME studies were available with the additive under assessment. The applicant submitted some studies carried out in rats after administering extracts of *E. senticosus* or its individual components.

Ma et al. (2013) gave orally to four groups of rats (six/group): (i) 5 mg/kg of sinapyl alcohol 4-*O*-glucoside or (ii) 4.5 mg/kg of (+)-syringaresinol-di-*O*-glucoside or (iii) the aqueous root extract of *E. senticosus* (at a dose containing 5 mg/kg sinapyl alcohol 4-*O*-glucoside and 4.5 mg/kg (+)-syringaresinol-di-*O*-glucoside) or (iv) the same dose of each isolated compound by intravenous injection. Blood was collected at several time points and the compounds were analysed by liquid chromatography tandem mass spectrometry (LC–MS/MS, LOQ: 1 ng/mL for both compounds). Absorption of the compounds was rapid, being T_{max} 0.45 h for isolated compounds and 0.58 h when present in the aqueous extract. The elimination half-life was lower than 2.5 h for both compounds and the bioavailability was 3.3% and 3.8% for sinapyl alcohol 4-*O*-glucoside and (+)-syringaresinol-di-*O*-glucoside, respectively. The area under the concentration-time curve from dosing (time 0) to time t (AUC_{0-t}) of sinapyl alcohol 4-*O*-glucoside and of (+)-syringaresinol-di-*O*-glucoside after oral administration of the aqueous extract was significantly higher as compared with the oral administration

[25] Technical dossier/Supplementary information August 2022/Taiga_root_tincture_literature_search.

of the single compounds. The mean plasma concentration–time curve of (+)-syringaresinol-di-*O*-glucoside after the oral administration of the extract suggested an enterohepatic circulation of this compound.

The pharmacokinetics of isofraxidin was investigated in rat after oral administration of 15 g/kg or 30 g/kg of *E. senticosus* root extract[26] or 7.5 or 15 mg/kg of isofraxidin. Isofraxidin, either given alone or in the extract, was rapidly absorbed (T_{max} of 0.20 and 0.30 h, respectively). Plasma C_{max} was approximately 7 or 14 μg/mL for the low and high doses, both when given as pure compound and in the extract (Sun et al., 2007a).

When *E. senticosus* root extract (15 g/kg) was administered orally to rats, eight compounds derived from the extract were detected in plasma, including sinapyl alcohol 4-*O*-glucoside (syringin) and isofraxidin. Three metabolites were identified as metabolites of sinapyl alcohol 4-*O*-glucoside, although the chemical structure was not elucidated (analysis by HPLC-UV with diode array detector) (Sun et al., 2007b).

After oral administration of an extract of *E. senticosus*[27] to rats, 11 metabolites of sinapyl alcohol 4-*O*-glucoside were detected in plasma and the structures of four of them were elucidated by ultra-performance liquid chromatoraphy coupled with quadrupole time-of-flight mass spectrometry (UPLC/Q-TOF MS) (Lu et al., 2012). Demethylation, oxidation, glucuronidation and acetylation after deglycosylation were the proposed metabolic pathways of sinapyl alcohol 4-*O*-glucoside.

Based on the above data, it is concluded that (+)-syringaresinol-di-*O*-glucoside and isofraxidin orally administered to rats are rapidly absorbed, attain very low plasma concentrations and there is some evidence of their extensive metabolism to conjugate derivatives after deglycosylation, demethylation and oxidation of the aglycones.

No ADME data of lignans and hydroxycoumarins in horses, dogs and cats were made available. Taking into account the *in vivo* experimental data in laboratory animals, the FEEDAP Panel assumes that in the target species these compounds are rapidly absorbed, metabolised and excreted, and are not expected to accumulate in animal tissues.

3.3.2. Genotoxicity

The genotoxic potential for syringaresinol and isofraxidin was predicted using the QSAR Toolbox.[28] No structural alerts were found for syringaresinol, whereas for isofraxidin structural alerts were due to coumarin structure. For syringaresinol and isofraxidin, the mutagenicity (Ames test) prediction was made by read-across analyses of data available for similar substances (i.e. analogues obtained by categorisation). Categories were defined using general mechanistic and endpoint profilers as well as empirical profilers. Mutagenicity read-across-based predictions were found to be consistently negative for all categories of analogues. On this basis, the alerts raised for isofraxidin were discounted. The predictions for syringaresinol and isofraxidin were considered to apply also to their glucosides (syringaresinol-di-*O*-glucoside and isofraxidin-7-glucoside).

These findings are in line with the negative results obtained in Ames and comet assays with syringaresinol or its metabolites (Hong and Lyu, 2013; Kirsch et al., 2020).

The literature search provided by the applicant also considered the genotoxicity of aqueous and ethanolic extracts obtained from *E. senticosus*.[25] Although the limited information submitted indicated no concern, the composition of the test items was unknow and major shortcomings in the study design were identified for all the studies provided (Hirosue et al., 1986; Park et al., 2006; Bespalov et al., 2013). Therefore, these studies were not considered relevant for the current assessment.

3.3.3. Toxicological studies

From the literature search provided by the applicant on the toxicology of preparations obtained from *E. senticosus*,[25] no studies were identified that could be used to derive a reference point for the safety assessment of taiga root tincture.

The toxicological dataset available for *E. senticosus* extracts has been reviewed by EMA (EMA, 2014a). Overall, the limited information available from repeated dose toxicity studies in laboratory animals and from reproductive and developmental studies did not show adverse effects of

[26] The extract contained 0.50 mg/g of isofraxidin, 0.06 mg/g of caffeic acid, 0.43 mg/g of eleutheroside B, 5.6 mg/g of chlorogenic acid, and 0.73 mg/g of eleutheroside D.
[27] The ethanol/water (80/20, v/v) extract contained 7.63% sinapyl alcohol 4-*O*-glucoside (w/w).
[28] Technical dossier/Supplementary information August 2022/Annex_XII_Eleutherococcus_QSAR.

E. senticosus extracts under the testing conditions (10 mg/kg bw per day). Similarly, no signs of toxicity were observed in clinical investigations performed with large numbers of patients.

3.3.4. Safety for the target species

In the absence of tolerance studies and/or toxicity data from repeated dose studies in laboratory animals performed with the additive under assessment, the approach to the safety assessment of the mixture is based on its individual components or groups of components. For the group assessment of coumarins and lignans, in the absence of data, the threshold of toxicological concern (TTC) is applied to derive maximum safe feed concentrations for the whole groups of compounds in the tincture (EFSA FEEDAP Panel, 2017b).

Coumarins

The additive under assessment contains on average 0.0007% hydroxycoumarins (up to 0.0009%). At the maximum proposed use level of 460.7 and 489.5 mg taiga root tincture/kg complete feed for dogs and cats, the highest concentration of hydroxycoumarins (≤0.0009% of the tincture) would be 0.004 mg/kg feed. For horses, at the maximum proposed use level of 140.7 mg/kg complete feed, the highest concentration of hydroxycoumarins would be 0.0013 mg/kg feed. The hydroxycoumarins isofraxidin and isofraxidin-7-glucoside were assigned to Cramer Class III. The available data indicate that their concentration would be considerably below the maximum acceptable concentration in feed for Cramer Class III (0.08 mg/kg feed for dogs and 0.07 mg/kg feed for cats and horses, EFSA FEEDAP Panel, 2017b). Therefore, no concern for the target species arises from hydroxycoumarins in taiga root tincture.

Lignans

The additive also contains on average 0.005% lignans (up to 0.009%). At the maximum proposed use levels of 460.7 and 489.5 mg taiga root tincture/kg complete feed for dogs and cats, the highest concentration of lignans (≤0.009% of the tincture) would be 0.041 mg/kg feed. For horses, at the maximum proposed use level of 140.7 mg/kg complete feed, the highest average concentration of lignans would be 0.012 mg/kg feed. All lignans were assigned to Cramer Class III. The available data indicate that their concentration would be below the maximum acceptable concentration in feed for Cramer Class III (0.08 mg/kg feed for dogs and 0.07 mg/kg feed for cats and horses, EFSA FEEDAP Panel, 2017b). Therefore, no concern for the target species arises from lignans in taiga root tincture.

3.3.4.1. Conclusions on safety for the target species

The additive is safe for dogs, cats and horses at the maximum proposed use level of 460.7, 489.5 and 140.7 mg/kg complete feed, respectively.

3.3.5. Safety for the consumer

There is no evidence for the use in food of taiga root tincture from *E. senticosus* in the Fenaroli's Handbook of Flavour Ingredients (Burdock, 2009).

Lignans and other phenolic compounds present in the additive will be readily metabolised and excreted and are not expected to accumulate in animal tissues and products. The same applies to hydroxycoumarins (see Section 3.3.1), which are present at very low concentrations in the additive (see Section 3.2.1). Therefore, the FEEDAP Panel considers it unlikely that the use of the additive in horse feed would result in a relevant uptake of the individual constituents by humans consuming horse meat.

Although there are no data on residues in horse meat of any of the constituents of the extract, consultation of the EFSA Comprehensive European Food Consumption Database (FoodEx2)[29] indicated that horse meat is consumed in Europe in a restricted number of countries,[30] by a low percentage of consumers[31] and in low amounts.[32] Therefore, given the low frequency of consumption of horse meat, the very low concentrations of secondary plant metabolites of taiga root in feed, the rapid excretion

[29] https://www.efsa.europa.eu/en/data-report/food-consumption-data#the-efsa-comprehensive-european-food-consumption-database

[30] Belgium, Finland, France, Italy, Netherlands, Portugal, Slovenia, Spain and Sweden, according to the FoodEx2.

[31] 0.1–2.8% of all subjects are consumers of horse meat in countries where it is consumed, according to the FoodEx2.

[32] On average 0.01–1.94 g/day, less than 1 kg/year when considering all subjects, and 10.75–226.25 g/day when considering consumers only (95th percentile).

and the expected limited retention of lignans and hydroxycoumarins in animal tissues (see section 3.3.1), the FEEDAP Panel considers that it is unlikely that the use of the additive would result in a relevant increase of the intake of the individual constituents by humans consuming products of animal origin (horse meat).

Consequently, no safety concern would be expected for the consumer from the use of taiga root tincture up to the use level in feed considered safe for horses.

3.3.6. Safety for the user

No specific data were provided by the applicant regarding the safety of the additive for users.

The applicant provided information according to Classification, Labelling and Packaging (CLP) Regulation (EC) 1,272/2008 [33] concerning the presence of ethanol in the tincture.[34]

In the absence of data, the additive under assessment should be considered as irritant to skin and eyes, and as a dermal and respiratory sensitiser.

3.3.7. Safety for the environment

E. senticosus is not native to Europe. Organic acids (oxalic acid and fumaric acid), simple phenols and lignans are components, which are present in many plants indigenous to Europe.

No environmental risk assessment is necessary for the use in dogs and cats (EFSA FEEDAP Panel, 2019).

At the maximum proposed use level of 140.7 mg/kg complete feed for horses, the concentration of coumarins in feed would be <0.0013 mg/kg. Since the concentration of total coumarins in feed is below 0.5 mg/kg, the threshold value for the predicted environmental concentration for soil (PEC_{soil}) of 10 μg/kg is not exceeded, and the use of the taiga root tincture from *E. senticosus* as a flavour in animal (horse) feed is not expected to pose a risk for the environment.

3.4. Efficacy

E. senticosus is not listed in the Fenaroli's Handbook of Flavour Ingredients or by FEMA as a flavouring agent.

However, the WHO monograph (WHO, 2002) and the Comments to the PhEur (2019) describe the root as having a strong characteristic aromatic flavour, with a bitter, acidic, and persistent taste. Overall, the FEEDAP Panel considers that *E. senticosus* can influence sensory properties of feedingstuffs.

4. Conclusions

Taiga root tincture from *E. senticosus* (Rupr. & Maxim.) Maxim. is safe for dogs, cats and horses at the maximum proposed use level of 460.7, 489.5 and 140.7 mg/kg complete feed, respectively.

The additive is considered safe for consumers when used at the proposed conditions of use in feed for horses.

The additive under assessment should be considered as irritant to skin and eyes, and as a dermal and respiratory sensitiser.

The use of taiga root tincture at the proposed use level in animal (horse) feed is not considered to be a risk for the environment.

It is recognised that the root of *E. senticosus* can influence sensory properties of feedingstuffs and no further demonstration of efficacy is considered necessary for the tincture under assessment.

[33] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1,355.

[34] Technical dossier/Supplementary information September 2021/Annex_XV_SIn reply_dong_quai_tincture_MSDS. H319: moderate eye irritation.

5. Documentation provided to EFSA/Chronology

Date	Event
28/10/2010	Dossier received by EFSA. Botanically defined flavourings from Botanical Group 02 - Apiales and Austrobaileyales for all animal species and categories. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)
09/11/2010	Reception mandate from the European Commission
26/02/2013	EFSA informed the applicant (EFSA ref. 7150727) that, in view of the workload, the evaluation of applications on feed flavourings would be re-organised by giving priority to the assessment of the chemically defined feed flavourings, as agreed with the European Commission
24/06/2015	Technical hearing during risk assessment with the applicant according to the "EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products": data requirement for the risk assessment of botanicals
17/06/2016	Technical hearing during risk assessment with the applicant according to the "EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products". Discussion on the ongoing work regarding the pilot dossiers BDG08 and BDG 09
27/04/2017	Trilateral meeting organised by the European Commission with EFSA and the applicant FEFANA on the assessment of botanical flavourings: characterisation, substances of toxicological concern present in the botanical extracts, feedback on the pilot dossiers
27/02/2019	Partial withdrawal by applicant (EC was informed) for the following additives: dill seed extract, celery seed extract (oleoresin), caraway oleoresin/extract, and opoponax oil
24/06/2019	Application validated by EFSA – Start of the scientific assessment
03/07/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: characterization, safety for the target species, safety for the consumer, safety for the user, safety for the environment*
30/09/2019	Comments received from Member States
22/08/2022	Reception of supplementary information from the applicant (partial dataset on taiga root tincture) - Scientific assessment remains suspended
31/10/2022	Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives – partial report related to nine additives (*dill herb oil, dill tincture, dong quai tincture, cumin oil, fennel tincture, parsley tincture, anise tincture, star anise tincture and ferula assa-foetida oil*)
16/12/2022	Reception of an addendum of the Evaluation report of the European Union Reference Laboratory for Feed Additives – final report related to 11 additives (*celery seed oil, caraway seed oil, coriander oil, taiga root tincture, fennel oil, common ivy extract (sb), ginseng tincture, anise oil, anise star oil, anise star terpenes and omicha tincture*)
19/01/2023	The application was split and a new EFSA-Q-2023-00032 was assigned to the preparation included in the present assessment
23/01/2023	Scientific assessment re-started for the preparation included in the present assessment
dd/02/2023	Opinion adopted by the FEEDAP Panel on taiga root tincture (EFSA-Q-2023-00032). End of the Scientific assessment for the preparation included in the present assessment. The assessment of other preparations belonging to BDG 02 is still ongoing

References

Bespalov VG, Aleksandrov VA, Semenov AL, Kovan'ko EG and Ivanov SD, 2013. Comparative effects of Difluoromethylornithine and Siberian ginseng root tincture on radiation-induced carcinogenesis in rats and their lifespan. Advances in Gerontology, 3, 70–76. https://doi.org/10.1134/S2079057013010049

Burdock GA, 2009. Fenaroli's handbook of flavor ingredients. 6th edn. CRC press. Taylor & Francis Group, Boca Raton, FL. https://doi.org/10.1201/9781439847503

Commentary on the PhEur, 2019. Arzneibuch-Kommentar. Gesamtwerk einschließlich 62. Aktualisierungslieferung 2019. Wissenschaftliche Verlagsgesellschaft Stuttgart. ISBN: 978-3-8047-3831-7, 2019

EFSA (European Food Safety Authority), 2012. Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements. EFSA Journal 2012;10(5):2663, 60 pp. https://doi.org/10.2903/j.efsa.2012.2663

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012a. Guidance for the preparation of dossiers for sensory additives. EFSA Journal 2012;10(1):2534, 26 pp. https://doi.org/10.2903/j.efsa.2012.2534

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012b. Guidance on studies concerning the safety of use of the additive for users/workers. EFSA Journal 2012;10(1):2539, 5 pp. https://doi.org/10.2903/j.efsa.2012.2539

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, López-Alonso M, López Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Anguita M, Galobart J and Innocenti ML, 2017a. Guidance on the identity, characterisation and conditions of use of feed additives. EFSA Journal 2017a;15(10):5023, 12 pp. https://doi.org/10.2903/j.efsa.2017.5023

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, López-Alonso M, López Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Anguita M, Galobart J, Innocenti ML and Martino L, 2017b. Guidance on the assessment of the safety of feed additives for the target species. EFSA Journal 2017b;15(10):5021, 19 pp. https://doi.org/10.2903/j.efsa.2017.5021

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, López-Alonso M, López Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Anguita M, Dujardin B, Galobart J and Innocenti ML, 2017c. Guidance on the assessment of the safety of feed additives for the consumer. EFSA Journal 2017c;15(10):5022, 17 pp. https://doi.org/10.2903/j.efsa.2017.5022

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, López-Alonso M, López Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Anguita M, Galobart J, Innocenti ML and Martino L, 2018. Guidance on the assessment of the efficacy of feed additives. EFSA Journal 2018;16(5):5274, 25 pp. https://doi.org/10.2903/j.efsa.2018.5274

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Bampidis V, Bastos M, Christensen H, Dusemund B, Kouba M, Kos Durjava M, López-Alonso M, López Puente S, Marcon F, Mayo B, Pechová A, Petkova M, Ramos F, Sanz Y, Villa RE, Woutersen R, Brock T, de Knecht J, Kolar B, van Beelen P, Padovani L, Tarres-Call J, Vettori MV and Azimonti G, 2019. Guidance on the assessment of the safety of feed additives for the environment. EFSA Journal 2019;17(4):5648, 78 pp. https://doi.org/10.2903/j.efsa.2019.5648

EFSA SC (EFSA Scientific Committee), 2009. Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements, on request of EFSA. EFSA Journal 2009;7(9):1249, 19 pp. https://doi.org/10.2093/j.efsa.2009.1249

EFSA SC (EFSA Scientific Committee), More SJ, Hardy A, Bampidis V, Benford D, Bennekou SH, Bragard C, Boesten J, Halldorsson TI, Hernandez-Jerez AF, Jeger MJ, Knutsen HK, Koutsoumanis KP, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Schlatter JR, Silano V, Nielsen SS, Schrenk D, Solecki R, Turck D, Younes M, Benfenati E, Castle L, Cedergreen N, Laskowski R, Leblanc JC, Kortenkamp A, Ragas A, Posthuma L, Svendsen C, Testai E, Dujardin B, GEN K, Manini P, Zare Jeddi M, Dorne J-LCM and Hogstrand C, 2019a. Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. EFSA Journal 2019;17(3):5634, 77 pp. https://doi.org/10.2903/j.efsa.2019.5634

EFSA SC (EFSA Scientific Committee), More S, Bampidis V, Benford D, Boesten J, Bragard C, Halldorsson T, Hernandez-Jerez A, Hougaard-Bennekou S, Koutsoumanis K, Naegeli H, Nielsen SS, Schrenk D, Silano V, Turck D, Younes M, Aquilina G, Crebelli R, Gürtler R, Hirsch-Ernst KI, Mosesso P, Nielsen E, Solecki R, Carfì M, Martino C, Maurici D, Parra Morte J and Schlatter J, 2019b. Statement on the genotoxicity assessment of chemical mixtures. EFSA Journal 2019;17(1):5519, 11 pp. https://doi.org/10.2903/j.efsa.2019.5519

EFSA SC (EFSA Scientific Committee), More SJ, Bampidis V, Benford D, Bragard C, Halldorsson TI, Hernandez-Jerez AF, Hougaard BS, Koutsoumanis KP, Machera K, Naegeli H, Nielsen SS, Schlatter JR, Schrenk D, Silano V, Turck D, Younes M, Gundert-Remy U, GEN K, Kleiner J, Rossi AM, Serafimova R, Reilly L and Wallace HM, 2019c. Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment. EFSA Journal 2019;17(6):5708, 17 pp. https://doi.org/10.2903/j.efsa.2019.5708

EMA (European Medicines Agency), 2014a. Committee on Herbal Medicinal Products (HMPC). Assessment report on *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim., radix. EMA/HMPC/680615/2013. Available online: https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-eleutherococcus-senticosus-rupr-et-maxim-maxim-radix_en.pdf

EMA (European Medicines Agency), 2014b. Committee on Herbal Medicinal Products (HMPC). Community herbal monograph on *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim., radix. EMA/HMPC/680618/2013. Available online: https://www.ema.europa.eu/en/documents/herbal-monograph/final-community-herbal-monograph-eleutherococcus-senticosus-rupr-et-maxim-maxim-radix_en.pdf

Hirosue T, Matsuzawa M, Kawai HH, Osogai Y, Yoshimura H and Takemoto K, 1986. Mutagenicity and subacute toxicity of *Acanthopanax senticosus* extracts in rats. Journal of Food Hygienic Society of Japan, 27, 380–386. https://doi.org/10.3358/shokueishi.27.380

Hong CE and Lyu SY, 2013. Evaluation of the mutagenic properties of two lignans from *Acanthopanax koreanum* Nakai. Toxicology Research, 29, 279–283. https://doi.org/10.5487/TR.2013.29.4.279

Kirsch V, Bakuradze T and Richling E, 2020. Toxicological testing of syringaresinol and enterolignans. Current Research in Toxicology, 1, 104–110. https://doi.org/10.1016/j.crtox.2020.09.002

Lu F, Sun Q, Bai Y, Bao S, Li X, Yan G and Liu S, 2012. Characterization of eleutheroside B metabolites derived from an extract of *Acanthopanax senticosus* Harms by high-resolution liquid chromatography/quadrupole time-of-flight mass spectrometry and automated data analysis. Biomedical Chromatography, 26, 1269–1275. https://doi.org/10.1002/bmc.2688

Ma B, Zhang Q, Liu Y, Li J, Xu Q, Li X, Yang X, Yao D, Sun J, Cui G and Ying H, 2013. Simultaneous determination of Eleutheroside B and Eleutheroside E in rat plasma by high performance liquid chromatography–electrospray ionization mass spectrometry and its application in a pharmacokinetic study. Journal of Chromatography B, 917–918, 84–92. https://doi.org/10.1016/j.jchromb.2012.12.041

Park SY, Lee SG, Kang SK and Chung SH, 2006. *Acanthopanax senticosus* reverses fatty liver disease and hyperglycemia in ob/ob Mice. Archives of Pharmacal Research, 29, 768–776. https://doi.org/10.1007/BF02974078

Sun H, Lv H, Zhang Y, Wang X, Bi K and Cao H, 2007a. Pharmacokinetics of isofraxidin in rat plasma after oral administration of the extract of *Acanthopanax senticosus* Using HPLC with solid phase extraction method. Chemical and Pharmaceutical Bulletin, 55, 1291–1295. https://doi.org/10.1002/jssc.200700265

Sun H, Lv H, Zhang Y, Meng X, Sui J, Wang X and Bi K, 2007b. HPLC method for preliminary analysis of constituents in rat blood after oral administration of the extract of *Acanthopanax senticosus*. Journal of Separation Science, 30, 3120–3126. https://doi.org/10.1002/jssc.200700265

PhEur (European Pharmacopoeia), 2020. Eleutherococcus (Eleutherococcus radix) European Pharmacopoeia, 10th Edition. Monograph 01/2008:1419. European Directorate for the Quality of Medicines and Health.

WHO (World Health Organization), 2002. WHO monograph on selected medicinal plants. Radix Eleutherococci., 2, 83–96.

Abbreviations

ADME	absorption distribution metabolism and excretion
AUC_{0-t}	area under the concentration-time curve from dosing (time 0) to time t
BDG	botanically defined group
bw	body weight
CAS	Chemical Abstracts Service
CDG	chemically defined group
CFU	colony-forming unit
DEET	diethyltoluamide
DM	dry matter
EC	European Comission
EEIG	European economic interest grouping
EMA	European Medicines Agency
EURL	European Union Reference Laboratory
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
FEMA	Flavour and Extract Manufactures Association
FFAC	Feed Flavourings authorisation Consortium of FEFANA (EU Association of Specialty Feed Ingredients and their Mixtures)
FLAVIS	The EU Flavour Information System
FL-No	FLAVIS number
FoodEx2	EFSA Comprehensive European Food Consumption Database
GC–MS	gas chromatography–mass spectrometry
HPLC	high-performance liquid chromatography
LC–MS–MS	liquid chromatography tandem mass spectrometry
LOQ	limit of quantification
PCBs	polychlorinated biphenyls
PCDD	polychlorinated dibenzo-*p*-dioxin
PCDF	and polychlorinated dibenzofuran
PEC_{soil}	predicted environmental concentration for soil
PhEur	European Pharmacopoeia
QSAR	Quantitative Structure–Activity Relationship

Q-TOF MS	quadrupole time-of-flight mass spectrometry
RH	relative humidity
sb	solvent-based
SC	EFSA Scientific Committee
TEQ	toxic equivalent
TTC	threshold of toxicological concern
UV	ultraviolet
UPLC	ultra-performance liquid chromatograph
WHO	World Health Organization