Safety of hot water extract of fruits and peduncles of Hovenia dulcis as a novel food pursuant to Regulation 1(EU) 2015/2283

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Safety of hot water extract of fruits and peduncles of *Hovenia dulcis* as a novel food pursuant to Regulation 1(EU) 2015/2283

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Abstract

Following a request from the European Commission, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on the safety of '*Hovenia dulcis* fruit extract' as a novel food (NF) for its use in food supplements. The NF concerns a hot water extract of sliced and dried fruits and peduncles of *Hovenia dulcis* Thun. The production process is described in sufficient detail but contains contradictory information regarding the mixing with another ingredient of the NF. The NF is comprised of mostly carbohydrates (about 90%), about 2% proteins, 5% moisture, less than 1% fat and about 2% ash. In addition, the NF contains small amounts of flavonoids such as dihydromyricetin, myricetin and quercetin. The Panel notes limitations of the data provided from the batch testing regarding proximate analyses and plant secondary metabolites. Given these limitations, the Panel considers that the data provided by the applicant do not demonstrate that different batches produced with the described production process meet the proposed specifications. The target population is the general adult population excluding pregnant and lactating women and people with a chronic disease, such as liver malfunction. Limited information was provided on a history of consumption of *Hovenia dulcis* fruits and on an extract approved in South Korea. A number of toxicological studies were performed. However, the study reports did not allow to verify that the test item was representative of the NF. The same applied to a human study provided by the applicant. The Panel concludes that the safety of the NF has not been established.

Keywords: *Hovenia dulcis*, hot water extract, novel food, ingredient, flavonoids

Requestor: European Commission following an application by Hovenia Dulcis AB

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1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

On 28 of April 2014, the company Hovenia dulcis AB submitted a request in accordance with Article 4 of the Novel Food Regulation (EU) 258/1997[1] to place on the market the dried fruit and peduncle extract of *Hovenia dulcis* Thunberg (HDFPE), as a novel food (NF) to be used in food supplements.

On 20 July 2017, the competent authority of Germany forwarded to the Commission its initial assessment report, which came to the conclusion that the NF did not meet the criteria for acceptance of a NF defined in Article (3)1 of Regulation (EU) 258/1997.

On 14 December 2017, the Commission forwarded the initial assessment report to the other Member States (MSs).

The concerns of a scientific nature raised in the initial assessment and by other MSs can be summarised as follows:

- The NF was inadequately characterised.
- Regarding the previous human exposure, the documents did not include any data on actual quantities consumed.
- The dose proposed and the intake of the NF had not been justified.
- Regarding the toxicological information, none of the reports contained precise information on the test material. In the study of subchronic toxicity, the applicant did not provide sufficient information to show that the test material used was representative of the NF.
- The potential allergenicity of the NF had not been well explored. No assessment of the botanical relationship between *Hovenia dulcis* fruits and other fruits known to cause allergic reactions in the European population had been undertaken which would have been a valuable indicator for potential cross reactivity to the food by allergic consumers.

According to Article 35 (1) of Regulation (EU) 2015/2283[2], any request for placing a novel food on the market within the Union submitted to a Member State in accordance with Article 4 of Regulation (EU) 258/1997 and for which the final decision has not been taken before 1 January 2018 shall be treated as an application under this Regulation.

In accordance with Article 10 (3) of Regulation (EU) 2015/2283, EFSA shall give its opinion as to whether the update of the Union List referred to in Article 10 (1) is liable to have an effect on human health.

2. Data and methodologies

2.1. Data

The safety assessment of this NF is based on data supplied in the application and information submitted by the applicant following two EFSA requests for supplementary information.

Administrative and scientific requirements for NF applications referred to in Article 10 of Regulation (EU) 2015/2283 are listed in the Commission Implementing Regulation (EU) 2017/2469[3].

A common and structured format on the presentation of NF applications is described in the EFSA guidance on the preparation and presentation of a NF application.[4] As indicated in this guidance, it is the duty of the applicant to provide all of the available (proprietary, confidential and published)

[1] Regulation (EU) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. OJ L 43, 14.2.1997, p. 1–6.

[2] Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001 (2013/0435 (COD). OJ L 327, 11.12.2015, p. 1–22.

[3] Commission Implementing Regulation (EU) 2017/2469 of 20 December 2017 laying down administrative and scientific requirements for applications referred to in Article 10 of Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. OJ L 351, 30.12.2017, pp. 64–71.

[4] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), Turck D, Bresson J-L, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst KI, Mangelsdorf I, McArdle H, Naska A, Neuhäuser-Berthold M, Nowicka G, Pentieva K, Sanz Y, Siani A, Sjödin A, Stern M, Tomé D, Vinceti M, Willatts P, Engel K-H, Marchelli R, Pöting A, Poulsen M, Salminen S, Schlatter J, Arcella D, Gelbmann W, de Sesmaisons-Lecarré A, Verhagen H and van Loveren H, 2016. Guidance on the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283. EFSA Journal 2016;14(11):4594, 24 pp. https://doi.org/10.2903/j.efsa.2016.4594

scientific data, including both data in favour and not in favour to supporting the safety of the proposed NF.

2.2. Methodologies

The assessment follows the methodology set out in the EFSA guidance on NF applications and the principles described in the relevant existing guidance documents from the EFSA Scientific Committee. The legal provisions for the assessment are laid down in Article 11 of Regulation (EU) 2015/2283 and in Article 7 of the Commission Implementing Regulation (EU) 2017/2469.

This assessment concerns only risk that might be associated with consumption of the NF under the proposed conditions of use, and is not an assessment of the efficacy of HDFPE with regard to any claimed benefit.

3. Assessment

3.1. Introduction

The NF is a hot water extract of dried fruits and peduncles of *Hovenia dulcis* Thunberg (family: Rhamnaceae), which is commonly named as Japanese raisin tree, Japanese cherry tree and Chinese raisin tree. *Hovenia dulcis* trees originate from China, Korea, Himalaya region and Japan and are cultivated in China, South America and Tanzania (Hyun et al., 2010). The NF is intended to be used as an ingredient for food supplements.

The applicant indicated that according to Regulation (EU) 2015/2283 this NF falls under the following categories:

(iv) 'foods and food ingredients consisting of or isolated from plants, except for foods and food ingredients obtained by traditional propagating or breeding practices and having a history of safe use'.

3.2. Identity of the NF

The NF is a hot water extract obtained from the dried fruits and peduncles of *Hovenia dulcis* Thunberg.

3.3. Production process

The fruits and peduncles are harvested manually in the wild in China in September and October. Once the fruits and peduncles are mature, they fall off the tree and the workers collect them by hand. After collection and sorting, the fruits and peduncles are packed in nylon bags of 25 kg and transported by ship to South Korea where they are screened for pesticide residues and other impurities.

Then they are stored frozen until they are sliced and dried in the dark, followed by an addition of water at a ratio of 1:10 (w/v). According to the applicant, the mixture of the dried slices and water is kept at a temperature of 110–150°C, preferably 120–125°C, and under a pressure ranging from 1 to 3 atm, optimally 1.5 atm, for 15 min to 48 h. In response to EFSA questioning, this wide range for the duration of the extraction, the applicant explained that the normal production schedule is between 15 min and 12 h and that due to weekends and holidays the schedule has to be adjusted and the extraction procedure will be different. After the extraction, the mixture is cooled, filtered and concentrated by evaporation at room temperature at ~1.5 atm to a solid content of 40%. In response to an EFSA question, the applicant informed that subsequently dextrin or maltodextrin is added at a ratio of 10:6 [extract:(malto)dextrin] to avoid clotting of the pure dried extract, before the mixture is spray-dried. The Panel notes discrepant information received from the applicant (i.e. file 'Reply on EFSA Risk Assessment 1' on the production process 4/5/2020 provides a Korean and an English package label which indicates 'Dextrin 37.5%', but the same file included also a copy of a certificate of analysis on a 'maltodextrin' product).

After addition of the dextrin/maltodextrin, the NF is delivered to Sweden in airtight polyethylene bags for encapsulation and packaging. The initial assessment raised concerns by a Member State regarding the use of ethanol in the production process, however, the applicant clarified that no ethanol is used. The applicant provided GMP certificates issued by the South Korean Ministry for Food and Drug Safety and the Korean Food and Drug Agency (KFDA) for the production of the ingredient and by Läkemedelsverket (Swedish Medical Products Agency) for the filling of capsules and packaging.

The Panel notes that no analytical data were provided on whether and to which degree the wide range of the extraction time (i.e. 15 min to 48 h) may impact the composition of the NF. It is also unclear whether the HDFPE is mixed with dextrin or maltodextrin. The Panel considers that the production process of the NF is not sufficiently described.

3.4. Compositional data

According to the application, the NF consists of a spray-dried mixture of 62.5% HDFPE and 37.5% dextrin or maltodextrin. The NF is comprised of mostly carbohydrates (about 90%), about 2% proteins, 5% moisture, less than 1% fat and about 2% ash; in addition, the NF contains small amounts (< 100 ppm) of flavonoids.

The applicant provided compositional information on *Hovenia dulcis* from the literature: Park et al. (2015) studied the content of four flavonoids in four batches of an extract obtained from the manufacturer of the NF with a high-performance liquid chromatographic (HPLC) method. That extract was produced of dried fruit powder extracted with hot water (100°C for 3 h) at a ratio at 1:40 (w/v). In addition to the differences of the processing of the raw material (i.e. powder) and the extraction conditions, also the further processing of the extract (centrifugation to remove insoluble particles) and the drying method (freeze-drying) differed from the production process of the NF. There is also no note on an addition of (malto)dextrin in this publication by Park et al. (2015). The results of this batch testing are provided in Table 1. Dihydromyricetin and taxifolin were the most abundant flavonoids in that extract.

Table 1: Contents of flavonoids in four batches of a *Hovenia dulcis* extract (mg/g) produced differently to the NF, published by Park et al. (2015) and measured by HPLC

Flavonoids (mg/g)	Batch No.			
	703	**701**	**0807-5**	**0807-6**
Dihydromyricetin	0.88 ± 0.05	1.19 ± 0.03	1.17 ± 0.03	0.33 ± 0.07
Taxifolin	0.86 ± 0.05	0.15 ± 0.01	0.93 ± 0.02	1.64 ± 0.01
Myricetin	0.17 ± 0.01	0.24 ± 0.01	0.06 ± 0.01	0.04 ± 0.01
Quercetin	0.13 ± 0.01	0.03 ± 0.00	0.04 ± 0.01	0.05 ± 0.01

HPLC: high-performance liquid chromatography.

Park et al. (2015) referred also to, but did not quantify, other components in the seeds or fruits of *Hovenia dulcis,* such as hovenodulinol, hovenitins I, II and III, (+)-3,3′,5′,5,7-pentahydroflavanone, laricitrin, myricetin, (+)-gallocatechin, dihydrokaempferol, saponin C2, β-daucosterol, hovenidulciosides A1, A2, B1 and B2, hodulosides I and III and hovenidulcigenin reported by Ding et al. (1997), ShuZhen et al. (2009), Yoshikawa et al. (1995, 1996, 1997) and Xu et al. (2003). In a letter to the applicant, EFSA noted scientific literature (Yoshikawa et al., 1996; Murakami et al., 1997) about other phenolic compounds and saponins present in the seeds and fruits of *Hovenia dulcis, some* of which may raise safety concerns at certain concentrations (Heim et al., 2002; Hobbs et al., 2013; Engen et al., 2015). The applicant did not address these concerns.

The applicant also provided information on other batches produced by the manufacturer of the NF in 2011 and 2013 and on batches produced in 2019. The certificates of analyses issued by the manufacturer of the NF for four different batches produced in 2011 and 2013 provided only information on moisture (ranging from 4.3% to 4.7%), quercetin (5.9–8.9 μg/g) and on some microbiological and chemical contaminants (Table 2).

Table 2: Results from testing of batches produced in 2011 and 2013 provided by the applicant

Parameter	Batch number*			
	LT111048P	**LT113028P**	**LT113027P**	**LT113026P**
	14 November 2011	**1 October 2013**	**30 September 2013**	**3 September 2013**
Moisture (%)	4.7	4.3	4.5	4.7
Quercetin (μg/g)	8.3	8.0	7.5	7.3
Total Aerobic Count (CFU/g)	5	25	5	5

Parameter	Batch number*			
	LT111048P	LT113028P	LT113027P	LT113026P
	14 November 2011	1 October 2013	30 September 2013	3 September 2013
Yeast and mould (CFU/g)	5	5	5	5
Coliforms (CFU/g)	Negative	Negative	Negative	Negative
Lead (ppm)	0.10	0.1	0.1	0.1
Mercury (ppm)	0.003	n.d.	n.d.	n.d.
Arsenic (ppm)	0.07	0.1	0.1	0.1
Cadmium (ppm)	0.01	n.d.	n.d.	n.d.

CFU: colony forming unit.
*: The date below the batch number is the production date; n.d. not detected.

Consequently, EFSA asked the applicant to provide more qualitative and quantitative data on the main constituents/proximate analyses of the NF (i.e. ash, moisture, protein, fat, and carbohydrates, flavonoids) and batch-to-batch analyses in order to show that these parameters meet the limits of the proposed specifications of the NF.

In response to this request, the applicant provided certificates of analyses from the manufacturer of the NF on five batches produced in 2019. The results are provided in Table 3.

Table 3: Results of batches produced in 2019 and certified by the manufacturer of the NF

Parameter	Batch number*				
	LT119027P	LT119037P	LT119043P	LT119044P	LT119046P
	31 July 2019	23 October 2019	28 November 2019	3 December 2019	26 December 2019
Moisture (%)	5.20	5.20	5.20	5.20	5.20
Protein (%)	2.34	2.34	2.34	2.34	2.34
Fat (%)	0.09	0.09	0.09	0.09	0.09
Carbohydrates (%)	91.40	91.40	91.40	91.40	91.40
Polysaccharides (mg/g)	185.17	185.17	185.17	185.17	185.17
Ash (%)	1.4	1.4	1.4	1.4	1.4
Sodium (mg/100 g)	20.97	20.97	20.97	20.97	20.97
Quercetin (μg/g)	8.49	7.94	7.94	7.99	8.74
Microbiology					
Aerobic counts (CFU)	< 1,000/g	< 1,000/g	< 1,000/g	< 1,000/g	< 1,000/g
***E. coli* (per 50 g)**	n.d.	n.d.	n.d.	n.d.	n.d.
Coliforms (CFU/g)	n.d.	n.d.	n.d.	n.d.	n.d.
Yeast and moulds (CFU/g)	n.d.	n.d.	n.d.	n.d.	n.d.
Heavy metals (ppm)**					
Lead	0.111	0.111	0.111	0.111	0.111
Mercury	0.001	0.001	0.001	0.001	0.001
Cadmium	0.001	0.001	0.001	0.001	0.001
Arsenic	0.080	0.080	0.080	0.080	0.080

NF: novel food; CFU: colony forming units.
*: The date below the batch number is the production date.
**: Not a specification parameter.

The Panel notes that the results of all tested parameters, except for quercetin (ranging from 7.94 to 8.74 μg/g), are identical for all five presented batches produced at different time points in 2019, which is considered unrealistic.

These five batches produced in 2019 and a sixth batch (LT119045P, production date not specified) were analysed by an external laboratory for their flavonoid content (Table 4).

Table 4: Flavonoid content of six batches produced by the manufacturer of the NF and certified by an external laboratory

Flavonoids (μg/g)	Batch no.					
	LT119027P 31 July 2019	LT119037P 23 October 2019	LT119043P 28 November 2019	LT119044P 3 December 2019	LT119045P no date	LT119046P 26 December 2019
Dihydromyricetin	n.d.	91.37	67.30	66.02	73.20	42.83
Taxifolin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Myricetin	12.08	36.69	27.96	28.05	30.04	27.35
Quercetin	5.18	3.39	4.64	5.13	4.47	4.46

n.d. not detected; NF: novel food.

The Panel notes that taxifolin could not be detected in these six batches and that the results for the contents of the other three flavonoids in these batches are up to more than 10-fold lower (for dihydromyricetin) than the results (presented in Table 1) obtained on an extract produced differently to the NF and which have been proposed by the applicant for setting specifications for dihydromyricetin, taxifolin and myricetin. The information from this external laboratory indicated that the analysed substance was a mixture consisting of 62.5% *Hovenia dulcis* extract and 32.5% dextrin vs. '37.5%' as indicated in the production process description in the application and as indicated on a product labelling provided by the applicant. Thus**,** it appears that the batches produced and tested in 2019 are not identical to the NF.

Another sample of a '*Hovenia dulcis* extract powder' (as stated by the applicant) and two samples of food supplements provided by the manufacturer of the NF (without further information on the tested material) were analysed by the external laboratories Eurofins and the Korean Health Supplements Institute. The proximate analyses (moisture, protein, fat, carbohydrates, ash) of these samples were within the proposed specification limits. Flavonoids were not analysed by these laboratories.

The Panel notes the concerns described above for the proximate analyses provided by the certificates of the manufacturer of the NF (i.e. identical figures) and regarding the identity of the analysed batches produced in 2019. Furthermore**,** the Panel considers that the NF is not sufficiently characterised regarding secondary plant metabolites.

3.4.1. Stability

No data regarding the stability of the NF were provided by the applicant.

3.5. Specifications

The specifications of the NF proposed by the applicant are presented in Table 5. They include the parameters for proximate analyses, flavonoids, heavy metals and microbiological specifications.

Table 5: Specifications of the NF proposed by the applicant

Parameter	Specification	Analytical method
Typical proximate analyses		
Moisture (%)	4–6	*
Protein (%)	1–3	*
Fat (%)	< 1	*
Carbohydrates (%)	89–94	*
Sugars (%)	18–21	*

Parameter	Specification	Analytical method
Ash (%)	1.0–2.5	*
Sodium (mg/100 g)	≤ 70	*
Flavonoids		
Quercetin (μg/g)	5.9–8.9	HPLC
Dihydromyricetin (mg/g)	0.33–1.19	HPLC
Taxifolin (mg/g)	0.15–1.64	HPLC
Myricetin (mg/g)	0.04–0.24	HPLC
Microbiological parameters		
Total aerobic count (CFU/g)	$< 5 \times 10^3$	*
Yeast and mould (CFU/g)	< 30	*
Coliforms (CFU/g)	< 10	*
***E. coli* (CFU/g)**	< 10	*
Coagulase-positive *Staphylococcus* (CFU/g)	< 10	*
***S. aureus* (CFU/g)**	< 10	*
Salmonella (CFU/g)	ND/25g	*
Heavy metals		
Lead (ppm)	< 1	*
Mercury (ppm)	< 0.1	*
Arsenic (ppm)	< 1	*
Cadmium (ppm)	< 1	*

*: No methods were proposed in section 'Specifications' by the applicant, CFU: colony forming unit, ND: not detected; HPLC: high-performance liquid chromatography; NF: novel food.

Given the limitations of the batch testing described in Section 3.4, the Panel considers that the data provided by the applicant do not demonstrate that different batches produced with the described production process meet the proposed specifications. It is also noted that the testing of batches produced in 2019 showed significantly lower contents of dihydromyricetin, taxifolin and myricetin (Table 4) as compared to the proposed specification limits for these flavonoids (Table 5) which were based on analyses of an extract, which was produced differently from the NF.

3.6. History of use of the NF and/or of its source

According to the applicant, literature (Bampi et al., 2010; Chau and Wu, 2006; Dieu, 1853; Eleotério et al., 2012; Lim, 2013; Martin-Garcia and Diez, 2012) demonstrates that *Hovenia dulcis* fruits are a commonly used food in Taiwan, Japan, China and Brazil.

Bampi et al. (2010), who studied the composition of *Hovenia dulcis* fruits and extracts and flour made of the fruits, noted that *Hovenia dulcis* is widely distributed in southern Brazil, but that there were no literature reports of its use in food products. According to two other references from Brazil, noted by the applicant, *Hovenia dulcis* is widespread in south Brazil but not well documented (Eleotério et al., 2012) and is considered as an invasive species (Martin-Garcia and Diez, 2012). The applicant has provided a reference for recipes with Hovenia dulcis fruits published in a Brazilian Blog (Sexta-Feira, 2008). According to Chau and Wu (2006), fruits and seeds of *Hovenia dulcis* can be used as a food ingredient in Taiwan, but not in China. Dieu (1853) noted in his medical and therapeutic compendium that fruits from *Hovenia dulcis* were tasting like pears when they are ripe, and that local Japanese called the tree 'Siku'.

According to a compendium by Lim (2013) on edible medicinal and non-medicinal plants, the ripe fruits and fruit peduncles are edible raw or cooked and can be used to make candies and substitutes for honey and wine; it also has been used as a traditional Chinese medicine for more than 1,000 years to treat alcohol abuse in China.

The applicant also provided an inventory handbook from the US Department of Agriculture on 'Perennial Edible Fruits of the Tropics' which indicates the peduncle of *Hovenia dulcis* as edible parts under the list of 'minor fruits' of Southeast Asia (USDA, 1987). 'Minor fruits' were defined as '[citation] *usually not widely distributed*. *They are often small. They may only grow wild and have little or no*

potential for cultivation and marketing. Most probably merit neglect, but some may have the potential to be improved and developed into a major fruit'.

The dossier contains a scientific article on dietary supplement use by South Korean adults based on data from the National Complementary and Alternative Medicine Use Survey in 2006 (Ock et al., 2010). According to this article, 5.2% of South Korean adults had consumed food supplements with 'Hovenia dulcis' in 2006. There was no information, however, in this article about the dose or duration of the intake or any other specific information on the consumption pattern or on the consumed supplements.

According to the applicant, *Hovenia dulcis* has been permitted for food use by the KFDA. The applicant also stated that *Hovenia dulcis* fruits and peduncles are consumed also as a fresh or dried fruit in Korea at an estimated quantity of 200,000 kg/year (no reference provided). The dossier also contains a table presenting 11 food products (eight beverages and three food supplements) from different companies with 'Hovenia dulcis extracts' on the market in South Korea (Table 6). According to the applicant, a product similar to the NF is already on the market in South Korea.

Table 6: Hovenia dulcis extract products on the market in South Korea in 2013

Type of Product	Country	Daily Dose	Yearly Total Consumption USD	Volume in Units
Beverage	Korea	140 mL (2,460 mg)	80,000,000	40,000,000 bottles
Beverage	Korea	100 mL (2,460 mg)	2,400,000	600,000 bottles
Tablet	Korea	2,460 mg/Tablet	60,000,000	600,000 boxes
Capsule	Korea	2,460 mg/Capsule	250,000	5,000 boxes
Tablet	Korea	2,460 mg/Tablet	360,000	6,000 boxes
Beverage	Korea	100 mL (1,000 mg)	24,000,000	6,000,000 bottles
Beverage	Korea	100 mL	75,000,000	18,750,000 bottles
Beverage (Tea Drinks)	Korea	350 mL or 500 mL	40,000,000	20,000,000 bottles
Beverage (Tea Drinks)	Korea	350 mL or 500 mL	25,000,000	16,600,000 bottles
Beverage (Tea Drinks)	Korea	500 mL	7,000,000	3,880,000 bottles
Beverage (Tea Drinks)	Korea	500 mL	5,000,000	2,500,000 bottles

3.7. Proposed uses and use levels and anticipated intake

3.7.1. Target population

The applicant intends to target the general adult population.

3.7.2. Proposed uses and use levels

The applicant intends to use the NF as an ingredient in food supplements in capsule or tablet form taken up to 6 times a day and with a maximum daily intake of 2.5 g.

3.7.3. Precautions and restrictions of use

According to the applicant, the NF is not recommended for children, pregnant women and individuals with chronic diseases such as liver malfunction. Following a request by EFSA to provide the rationale for these restrictions of use, the applicant indicated that no studies have been performed on pregnant women and children and that recommendations of the Swedish Food Administration regarding food supplements were followed.

3.8. Absorption, distribution, metabolism and excretion

No studies on the absorption, distribution, metabolism and excretion (ADME) of the NF or any constituent thereof were provided by the applicant. The applicant argued that the macronutrients of the NF are expected to be digested according to the usual digestion and absorption routes.

3.9. Nutritional information

Considering the compositional data as provided by the applicant and as presented in Section 3.4 (Composition) and the maximum daily intake per day of 2.5 g, the Panel considers that consumption of the NF is not nutritionally disadvantageous.

3.10. Toxicological information

The applicant has provided an acute toxicity study in rats (Biotoxtech, 2002a), a bacterial reverse mutation test (Biotoxtech, 2002b; unpublished), an *in vivo* micronucleus test in mice (Biotoxtech, 2002c; unpublished), a chromosome aberration test with hamster lung cells (Biotoxtech, 2002d; unpublished) and a 90-day subchronic rat study, (Biotoxtech, 2003; unpublished). According to the applicant, these studies followed KFDA Guidelines for Good Laboratory Practice (GLP). The study reports of these toxicological tests indicate that '*Hovenia Dulcis Fruit Extracts*' was the test substance and describe it as a 'dark brown powder', but they also indicated that '[citation] *other information such as identity, strength, purity and stability was not provided*'.

In two letters to the applicant, EFSA expressed concerns on the genotoxicity testing strategy applied by the applicant and on the representativeness of the material tested in the toxicological studies. In order to address these concerns, EFSA asked the applicant to provide an *in vitro* mammalian cell micronucleus test performed in accordance to OECD TG 487 and in line with the tiered genotoxicity testing strategy as indicated by the EFSA Scientific Committee (2011) and by the EFSA NDA Panel (2016), and an *in vitro* mammalian cell gene mutation test performed in accordance to OECD TG 476. EFSA suggested to the applicant to consider the EFSA Scientific Committee Statement (2019) on genotoxicity assessment of chemical mixtures in particular chapter 2.1.1 ('Mixtures containing a substantial fraction of unidentified components') and chapter 2.3 ('Genotoxicity assessment of mixtures containing a substantial fraction of unidentified components') for these two requested tests.

Regarding the provided toxicological studies, EFSA asked the applicant to provide information on the test substance in order to demonstrate that it met the compositional characteristics and specification limits of the NF. EFSA also noted to the applicant the OECD GLP Guidance requirement that evaluations of chemicals should be based on safety test data of sufficient quality, rigour and reproducibility (OECD, 1998). According to the OECD Guidance documents 487 (OECD, 2016) and 408 (OECD, 2018), study reports should include comprehensive qualitative and quantitative physicochemical information on the identity and characterisation of the test item.

In his response, the applicant provided a letter signed by the chief executive officer (dated 25/10/2017) which stated that '[citation] *This is to confirm that the Hovenia Dulcis Extract substance used in the application for a Novel Food application to EFSA, submitted by Hovenia Dulcis AB, Sweden is the same as in the KFDA application for an approval for food supplements referred to in the submitted documents. The substance has also been used in the toxicological studies performed by Biotoxtech Inc. which are reported in the application*'. However, no data regarding the compositional characteristics and specification parameters of the material tested in the toxicological studies were provided by the applicant.

The Panel notes that the letter provided by the applicant does not allow EFSA to validate that the identity of the test substance and its physicochemical composition are representative for the NF. Consequently, the Panel considers that the provided toxicological study reports are not informative for the assessment of the toxicological properties of the NF.

3.10.1. Human data

Two human studies in adults and a report on a paediatric case of toxic hepatitis associated with the consumption of products obtained from *Hovenia dulcis* were provided.

An unpublished report summarised a double-blinded, placebo-controlled trial with 74 subjects aged 18–70 years with alcohol-induced liver damage (inclusion criterion: γ-glutamyl transpeptidase (γ-GTP) ≥ 60) who either received three times per day 900 mg of a 'Hovenia dulcis berry extract powder' produced by the manufacturer of the NF or placebo for 12 weeks (Lifetree Biotech, undated). The trial was conducted in 2007–2008. The Panel notes that the study report did not provide information (e.g. certificate of analysis, any compositional characteristic of the NF) which would allow to verify that the test item was representative for the NF. The Panel considers therefore that this human study is not informative for the assessment of the safety of the NF.

The second human study used a hot water extract of *Hovenia dulcis* fruits (boiled for 4 h) produced by the manufacturer of the NF which met the specifications for quercetin of the NF (i.e. 5.9–8.9 μg/g) (Kim et al., 2017). It was a randomised controlled crossover trial with 26 male adults with a mean age of 24 years who received a single dose of 2.5 g of the NF together with 360 mL of Korean Soju (17.5% v/v alcohol) in order to evaluate effects of the NF on 'hang over' symptoms. The Panel notes the limitations of this study for its use to assess the safety of the NF (i.e. single dose, low number of subjects, co-consumption with alcohol and the study objective) and considers that this study is not relevant for the safety assessment of the NF.

The case report concerned a 3.6-year-old boy who had consumed water boiled with *Hovenia dulcis* daily (plant part not specified) for about a year prior to the diagnosis of a severe toxic hepatitis and was evaluated for liver transplantation (Kim et al., 2012). There was no further information about the amount of beverage ingested, the concentration of *Hovenia dulcis* fruits in the beverage. According to the authors, the case was classified 'probable' causally related to the consumption of *Hovenia dulcis*. The Panel notes that case reports *per se* are not suitable to establish a cause and effect relationship. There is no information available on how the consumed item relates with the composition and proposed intake level of the NF, thus the relevance of this paediatric case remains unclear.

3.11. Allergenicity

According to the proposed specifications, the NF contains 1–3% protein. According to the applicant, there are no reports on allergic reactions associated with *Hovenia dulcis* fruits although more than 750 million 'products' of *Hovenia dulcis* fruit extract have been consumed since the substance was approved by the KFDA in 2008. The applicant also noted that he could not identify reports concerning allergenicity from China, Japan and Brazil where the fruit is consumed.

4. Discussion

The NF concerns a hot water extract from the ripe fruits and peduncles of *Hovenia dulcis* Thunb. collected from the wild in China. The Panel considers that the proposed specifications are not supported by an appropriate compositional characterisation and by batch testing.

The applicant has provided some information on a history of consumption of *Hovenia dulcis* fruits and extracts in foods, mainly beverages and food supplements, and in the traditional Chinese medicine in countries in South Asia.

The application includes study reports on an acute toxicity study, a bacterial reverse mutation test, an *in vivo* micronucleus test, a chromosome aberration test and a 90-day subchronic toxicity study in rats. The genotoxicity studies provided by the applicant do not comply with EFSA Guidance documents, as an *in vitro* micronucleus test is missing. In addition, the studies provided did not include information that permitted the identification and characterization of the test substance.

Consequently, the Panel considers that the provided toxicological study reports are not informative for the assessment of the toxicological properties of the NF and cannot be used to derive safe intake levels for human consumption. Similarly, an unpublished study report on a human trial for 12 weeks did not provide information which would allow to verify that the test item was representative for the NF. Another human trial concerning the effect of a single dose of 2.5 g of the NF on hang-over symptoms is considered not relevant for the safety assessment of the NF.

5. Conclusions

The Panel concludes that the safety of the NF has not been established.

Steps taken by EFSA

1) Letter from the European Commission to the European Food Safety Authority with the request for a scientific opinion on the safety of *Hovenia dulcis* fruit extract as a novel food Ref. ARES(2018)5373981 dated 19.10.2018.
2) On 19.10.2018, EFSA received a valid application from the European Commission on *Hovenia dulcis* fruit extract as a novel food, which was submitted by Hovenia dulcis AB, and the scientific evaluation procedure started.

3) On 18.01.2019, 08.03.2019, 11.03.2019 and 29.05.2019 EFSA requested the applicant to provide additional information to accompany the application and the scientific evaluation was suspended.
4) On 07.03.2019, 11.03.2019, 12.03.2019 and 04.05.2020 additional information was provided by the applicant and the scientific evaluation was restarted.
5) During its meeting on 30.06.2020, the NDA Panel, having evaluated the data, adopted a scientific opinion on the safety of *Hovenia dulcis* fruit extract as a novel food pursuant to Regulation (EU) 2015/2283.

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Abbreviations

ADME	absorption, distribution, metabolism and excretion
CFU	colony forming unit
GLP	good laboratory practice
GMP	Good Manufacturing Practices
HDFPE	*Hovenia dulcis* fruit and peduncle extract
HPLC	high-performance liquid chromatography
ICP-MS	induced coupled plasma-mass spectrometry
KFDA	Korean Food and Drug Agency
MSs	Member States
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NF	novel food
OECD	Organisation for Economic Co-operation and Development
USDA	United States Department of Agriculture