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Safety of water extract of *Cistanche tubulosa* stems as a Novel food pursuant to Regulation (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 water extract of *Cistanche tubulosa* stems as a novel food (NF) for its use in food supplements (FS) and foods for special medical purposes (FSMP). The target population is the general adult population excluding pregnant and lactating women. The applicant proposes a maximum daily intake of 2 g for FS and a maximum use level of 10% in FSMP. The characteristic components of the extract are phenylethanoid glycosides (at least 70% of the NF), in particular, echinacoside (25–45% of the NF). The NF has been authorised as a prescription drug in China in 2005 for the treatment of vascular dementia. The Panel notes that an integrated analysis of three studies covering 1,076 patients with vascular dementia treated with the proposed NF at a daily dose of 1,800 mg, reported that 12 adverse events (AEs) were classified to be 'definitely', 'probably' or 'possibly related' to the exposure to the NF. Two of these AE were classified as severe (cerebral haemorrhage and epilepsy). The Panel considers that the reported AEs raise safety concerns. The Panel also notes the limitations of the provided toxicological studies, in particular the non-compliance with the EFSA approach on the genotoxicity testing strategy and the non-compliance with good laboratory practice (GLP) and the respective OECD Guidance documents of the repeated dose toxicity studies. In view of the AEs in the human studies, the Panel considers that additional toxicological studies, following testing guidelines would not be able to overcome the concerns raised from the human studies. The Panel concludes that the safety of the NF has not been established.

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1. Introduction

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

On 01 October 2019, the company Sinphar Tian-Li Pharmaceutical Co., Ltd. submitted a request to the European Commission in accordance with Article 10 of Regulation (EU) 2015/2283¹ to authorise the placing on the Union market of *Cistanche (C.) tubulosa* extract as a novel food (NF).

The application requests to authorise the use of *C. tubulosa* extract in food supplements and food for special medical purposes. The applicant has also requested data protection under Article 26 of Regulation (EU) 2015/2283.

In accordance with Article 10(3) of Regulation (EU) 2015/2283, the European Commission asks the European Food Safety Authority to provide a scientific opinion on *C. tubulosa* extract as a NF.

In addition, the European Food Safety Authority is requested to include in its scientific opinion a statement as to if, and if so to what extent, the proprietary data for which the applicant is requesting data protection was used in elaborating the opinion in line with the requirements of Article 26(2)(c) of Regulation (EU) 2015/2283.

2. Data and methodologies

2.1. Data

The safety assessment of this NF is based on data supplied in the application.

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) 2017/2469¹.

A common and structured format on the presentation of NF applications is described in the EFSA guidance on the preparation and presentation of an NF application (EFSA NDA Panel, 2016). As indicated in this guidance, it is the duty of the applicant to provide all of the available (proprietary, confidential and published) scientific data (including both data in favour and not in favour) that are pertinent to the safety of the NF.

This NF application includes a request for protection of proprietary data in accordance with Article 26 of Regulation (EU) 2015/2283. The data requested by the applicant to be protected comprise all toxicological and human studies of this application.

2.2. Methodologies

The assessment follows the methodology set out in the EFSA guidance on NF applications (EFSA NDA Panel, 2016) 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 the risks that might be associated with consumption of the NF under the proposed conditions of use, and is not an assessment of the efficacy of the NF with regard to any claimed benefit.

3. Assessment

3.1. Introduction

The NF which is the subject of the application is a water extract of the stems of *C. tubulosa* cultivated in China. It contains at least 70% phenylethanoid glycosides. The NF is intended to be used as an ingredient for food supplements and foods for special medical purposes. The target population is the general adult population excluding pregnant and lactating women.

3.2. Identity of the NF

The NF is a water extract obtained from the dried stems of *C. tubulosa* (Schenk) Wight.

¹ 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.

3.3. Production process

The cultivation of *C. tubulosa* requires first the cultivation of the host plant *Tamarix chinensis* which is then inoculated with the parasitic plant *C. tubulosa*. After harvesting of *C. tubulosa*, the stems are washed, cut into slices and dried. The production process of the NF comprises extraction with water, concentration, precipitation with ethanol and spray drying steps.

3.4. Compositional data

According to proximate analyses of two batches, the NF contains approximately 93 g carbohydrates of which about 1.3 g is fibre, 1.5 g protein, 1.3 g lipids, 3.2 g moisture and 0.2 g ash per 100 g. The major component of the extract is a group of phenylethanoid glycosides (at least 70% of the NF) and in particular echinacoside (25–45% of the NF). In addition to echinacoside, other phenylethanoid glycosides identified in the NF are: 2'-acetylacteoside, acteoside, campneoside I, campneoside II, cistantubuloside A, cistantubulosides B1, B2, cistantubulosides C1, C2, crenatoside, decaffeoylacteoside, echinacoside, isoacteoside, rhodiolide, syringalide A 3'- α -L-rhamnopyranoside and tubuloside A.

The applicant has provided the results of seven batches which showed contents of phenylethanoid glycosides and echinacoside ranging between 73.5% and 79.8% and 31.9% and 38.9%, respectively.

These seven batches have also been analysed for solvents residuals, heavy metals and microbiological parameters. Additional testing on some batches of the raw material as well as of the NF was performed for pesticides and aflatoxins.

3.4.1. Stability

The applicant performed a 48-month (25°C/RH 60%) and an accelerated 6-month (40°C/RH 75%) stability testing on six batches. At the end of the 48 months, the phenylethanoid glycosides and echinacoside ranged between 70.1% and 79.1% and 30.1% and 37.1%, respectively. At the end of the 6 months under accelerated storage conditions, the ranges were 71.3–75.3% and 28.0–35.1, respectively.

3.5. Specifications

The specifications of the NF as proposed by the applicant are indicated in Table 1.

Table 1: Specifications of the NF

Parameter	Specification	Analytical method
Appearance	Greyish brown to dust brown powder	Visual
Identification	Conforms with standards	Chinese Pharmacopeia, 2015 edition, vol. IV, Method 0502
Loss on drying	≤ 5.0%	Chinese Pharmacopeia, 2015 edition, vol. III, Method 0831
Particle size	100% pass through 60 mesh (250 micron)	Chinese Pharmacopeia, 2005 edition, vol. IV, Method 0982
Sulfated ash	≤ 2.5%	Chinese Pharmacopeia, 2015 edition, vol. III, Method 0841
Echinacoside	≥ 25.0% to 45.0%*	HPLC, in house method
Phenylethanoid glycosides	≥ 70.0%*	
Heavy metals		
Arsenic	≤ 0.5 mg/kg	Hydride atomic spectrometry
Lead	≤ 0.3 mg/kg	Graphite furnace atomic absorption spectrometry
Mercury	≤ 0.1 mg/kg	Chinese Pharmacopeia, 2015 edition, vol. III, Method 2321
Cadmium	≤ 0.2 mg/kg	Chinese Pharmacopeia, 2015 edition, vol. III, Method 2321

Parameter	Specification	Analytical method
Residual solvents		
Benzene	≤ 2 mg/kg	GC, in house method
Ethanol	≤ 5,000 mg/kg	
Divinylbenzene	≤ 0.05 mg/kg	
Methanol	≤ 5 mg/kg	
Microbial parameters		
Total aerobic plate count	≤ 1,000 CFU/g	Chinese Pharmacopeia, 2015, edition, vol. I, appendix X III C
Moulds	≤ 25 CFU/g	
Yeasts	≤ 25 CFU/g	
E. coli	Negative	
Salmonella	Negative	
Coliform	Negative	
Staphylococcus	Negative	
Others		
Mycotoxins (aflatoxins)	Negative	USP 30
Pesticides	Negative	GB/T 19648-2006**

CFU: Colony forming unit; HPLC: High-performance liquid chromatography; GC: Gas chromatography; USP: United States Pharmacopeia.

*: Assay on a dry basis.

**: Chinese national standard: <https://www.chinesestandard.net/PDF/English.aspx/GBT19648-2006>

The Panel notes the specification parameter 'benzene', which is genotoxic and carcinogenic.

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

3.6.1. History of use of the source

According to the applicant, the plant has a long history of use in Asia, especially in traditional Chinese medicine. The applicant also provided information that the root of *C. tubulosa* is used as one of the 'drug and health products' in Canada (Health Canada, 2019).

3.6.2. History of use of the NF

According to the applicant, the extract is authorised in Taiwan for food use with a maximum daily dose of 450 mg (Taiwan Food and Drug Administration, 2017). It has been granted marketing authorisation as a prescription drug in China in 2005 for the treatment of vascular dementia.

3.7. Proposed uses and use levels and anticipated intake

3.7.1. Target population

The target population proposed by the applicant is the general adult population excluding pregnant and lactating women. 'Insufficient data' for these subpopulation groups were reasoned for their exclusion.

3.7.2. Proposed uses and use levels

The applicant proposes the use of the NF for food supplements at a use level of 2 g/day and for foods for special medical purposes (FSMP) at 100 g/kg food. No maximum daily intake of the NF was proposed for FSMP.

3.8. Absorption, distribution, metabolism and excretion (ADME)

A literature search by the applicant identified seven studies published in seven articles related to ADME and *C. tubulosa* stem extracts. These studies included information on *in vitro* models (Li et al., 2016a, 2017) to study metabolites of echinacoside, cistanoside, acteoside and isoacteoside echinacoside and rat models (Jia et al., 2006; Wang et al., 2009; Cui et al., 2016; Li et al., 2016a,b; Qi et al., 2013) to

study the bioavailability, distribution, metabolism and elimination of some phenylethanoid glycosides such as echinacoside, acteoside and isoacteoside.

3.9. Nutritional information

Considering the proximate analyses provided in Section 3.4 (Compositional data), the Panel considers that consumption of 2 g of the NF per day is not nutritionally disadvantageous.

3.10. Toxicological information

The applicant provided several toxicological studies, according to the applicant all of them were performed with the NF, but this is not evidenced by information contained in the study reports.

Genotoxicity was studied in four bacterial reverse mutation tests (Hunan Provincial Center For Disease Control and Prevention, 2005; Development Center for Biotechnology, 2008a; Hubei Provincial Center For Disease Control and Prevention, 2010a; Liao et al., 2018), in one *in vitro* chromosomal aberration test (Liao et al., 2018), and in two *in vivo* mouse micronucleus tests (Development Center for Biotechnology, 2008b; Hubei Provincial Center For Disease Control and Prevention, 2010b).

Regarding animal testing, the applicant provided one acute study in mice (Hubei Provincial Center For Disease Control and Prevention, 2010b), two subacute toxicity studies in rats (Hunan Provincial Center For Disease Control and Prevention, 2005; Liao et al., 2018), one subchronic toxicity study in rats (Hubei Provincial Center For Disease Control and Prevention, 2010b) and 6-month studies in rats and dogs aimed to study chronic toxicity and carcinogenicity (Peking University School of Pharmaceutical Sciences, 1998a,b.)

The Panel notes that the genotoxicity testing strategy did not comply with the EFSA Guidance which requests a tiered approach to address genotoxicity in a first step with a bacterial reverse mutation test and an *in vitro* micronucleus test (EFSA Scientific Committee, 2011). The Panel also considers that acute toxicity studies are not pertinent for the safety assessment of NFs. Furthermore, none of the repeated dose toxicity studies are in compliance with good laboratory practice (GLP) and respective OECD Guidance documents. This applies also to the subchronic toxicity study which was insufficiently described in eight pages in an unpublished report by the Hubei Provincial Center for Disease Control and Prevention (2010b).

3.10.1. Human data

The applicant has presented four human studies conducted with the NF summarised in Table 2.

Table 2: Summary of human data

Study design	Study population	Number of subjects ^(a)	Duration of study	Treatment
Open label 1-arm ^(b)	Patients with moderate Alzheimer's Disease	18	48 weeks	Test item: 2 × 300 mg NF TID (1,800 mg per day)
Phase II ^(c) RCT, double-blind	Vascular dementia patients	115/112 (test/control)	Each 3 months	Test item: 2 × 300 mg NF TID (1,800 mg per day)
Phase III ^(c) RCT, open-label		330/111 (test/control)		Control item: 2 × 1 mg Ergoloid mesylates TID (6 mg per day)
Phase IV ^(c) Open-label 1-arm		625		Test item: 2 × 300 mg NF TID (1,800 mg per day)

TID: three times a day.

(a): Number of subjects who completed the trial.

(b): Guo et al. (2013).

(c): Sinphar (2011).

One article was provided on an uncontrolled open-label trial with 18 patients suffering from moderate Alzheimer's Disease treated with two capsules of 300 mg of the NF three times a day (total daily dose of 1,800 mg) for 48 weeks (Guo et al., 2013). Safety relevant endpoints were vital signs (blood pressure, heart rate and body weight); haematological parameters (white blood cell total count and differential count, haemoglobin, red blood cell count and platelet count) and blood chemistry,

electrocardiography (ECG); and adverse events (AEs). At week 24, 36 and 48, diastolic blood pressure was reported to be statistically significant lower by 6–7 mm Hg as compared to week 0. One patient reported nausea after 8 weeks and one patient had hallucinations at the beginning of the study and a recurrence at week 12. One and three patients showed an increase (figures not provided) of alanine aminotransferase (ALT) at week 24 and week 48, respectively. All AEs were reported to be mild by the authors. The Panel notes the uncontrolled study design and considers that no conclusions can be drawn on whether or not the reported AEs were causally related to the treatment.

In addition, the applicant also provided an integrated analysis of the safety data from three clinical trials (phase II, III and IV) in patients suffering from vascular dementia (Sinphar, 2011). This report analysed the AEs reported in these three trials with 3-month duration. It covered the safety data of 1,076 patients who received the NF at a daily dose of 1,800 mg in these three trials in comparison to the safety data of 229 patients (comparator group) treated with 6 mg per day of ergoloid mesylates (a mixture of three ergot alkaloids) in the two controlled trials (i.e. phase II and phase III trials).

Throughout these three studies, 46 subjects experienced 49 AEs. The occurrence rate of AEs was 3.72% (n = 40) for the NF group and 3.93% (n = 9) for the comparator group. Six of in total eight AEs classified as 'severe' occurred in the NF group, which represents an occurrence rate similar for both groups. Among the 40 AEs which were reported for the NF group, the study principal investigators considered that one was considered '*definitely related*' to the NF (gastritis of moderate degree), three AEs were considered '*probably related*' to the NF (constipation of moderate degree, epilepsy of severe degree and mild sleepiness) and eight AEs were classified as '*possibly related*' to the NF (cerebral haemorrhage of severe degree, gastric haemorrhagic ulcer and lethargy of moderate degree, twice constipation, each once dizziness, fatigue and sleepiness of mild degree). The occurrence rate of AEs that were considered definitely, probably or possibly related to the treatment with the NF was about 1.1%. According to the authors of this integrated analysis, the *C. tubulosa* stem extract appeared to be '*reasonably safe*' for the study population, i.e. patients suffering from vascular dementia. This report also referred to a 5-year Periodic Safety Update Report for the item authorised as prescription drug in China for the treatment of vascular dementia, indicating that for the 844 patients treated since the marketing approval in 2005, no AE has been reported.

4. Discussion

The Panel notes that an integrated analysis of three human studies covered 1,076 patients with vascular dementia treated with the proposed NF at a daily dose of 1,800 mg. The Panel also notes that the approach to evaluate the safety in human and the design of the human studies (especially the use of an approved drug as a comparator in the phase II and phase III studies) followed the general approach taken for the clinical development of a drug, rather than a novel food. The use of a drug as a comparator instead of a placebo control limits the conclusions that can be drawn from such studies for the safety assessment of an NF. While the purpose of evaluating the safety of a drug is to support the risk–benefit assessment for a specific patient group, randomised controlled human trials that address the safety of NFs should rather employ a placebo control and ideally the general population.

Different to the considerations made by the applicant in the integrated analyses of the three trials with patients suffering from vascular dementia and who considered that the item was safe for such patients, the Panel is assessing the safety of the NF for the general adult population without taking into account potential benefits. The Panel notes the occurrence of 12 (1.1%) AEs across three studies covering 1,076 subjects which were judged by the principal study investigator to be '*definitely*', '*probably*' or '*possibly related*' to the treatment with the NF. Two of these AEs were classified as severe (cerebral haemorrhage and epilepsy). The Panel considers that the reported AEs raise safety concerns.

The Panel also notes the limitations of the provided toxicological studies, in particular the non-compliance with the EFSA Guidance on the genotoxicity testing strategy and the non-compliance with GLP and the respective OECD Guidance documents of the repeated dose toxicity studies. In view of the AEs in the human studies, the Panel considers that additional toxicological studies, following testing guidelines would not be able to overcome the concerns raised from the human studies.

5. Conclusions

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

6. Steps taken by EFSA

- 1) On 29/05/2020 EFSA received a letter from the European Commission with the request for a scientific opinion on the safety of water extract of *Cistanche tubulosa* stems, Ref. Ares (2020) 2872765 – 03/06/2020.
- 2) On 29/05/2020, a valid application on water extract of *Cistanche tubulosa* stems, which was submitted by name of the company, was made available to EFSA by the European Commission through the Commission e-submission portal (NF2019/1318) and the scientific evaluation procedure was initiated.
- 3) During its meeting on 24 November 2020, the NDA Panel, having evaluated the data, adopted a scientific opinion on the safety of water extract of *Cistanche tubulosa* stems as a NF pursuant to Regulation (EU) 2015/2283.

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Abbreviations

ADME	absorption, distribution, metabolism and excretion
AEs	adverse events
ALT	alanine aminotransferase
CFU	colony-forming units
ECG	electrocardiography
FS	Food supplements
FSMP	food for special medical purposes
GC	gas chromatography
GLP	Good Laboratory Practice
HPLC	high-performance liquid chromatography
NDA	Panel on Nutrition, Novel Foods and Food Allergens
NF	novel food
OECD	Organisation for Economic Co-Operation and Development
RH	relative humidity
SC	Scientific Committee
TID	three times a day
TLC	thin layer chromatography
USP	United States Pharmacopeia