Report of the Scientific Committee of the Spanish Agency for Consumer Affairs, Food Safety and Nutrition (AECOSAN) on the risk of using *Tribulus terrestris* in food supplements

Section of Food Safety and Nutrition

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Abstract

Tribulus terrestris L. is a plant from the Zygophyllaceae family whose use in food supplements is authorised in various countries of the European Union. In its natural form, it contains various active substances, the most notable of which are steroidal saponins, β-carboline alkaloids, flavonoids and lignanamides.

Tribulus terrestris' toxicity to animals has been widely documented throughout its history as a medicinal plant and it has been reported to have negative neuronal, muscular, hepatic and renal effects.

Some countries consider using parts of the *Tribulus terrestris* plant to produce food supplements to be unsafe, so they do not allow such supplements to be sold. This is reported through the European Rapid Alert System for Food and Feed (RASFF).

The Scientific Committee has conducted a risk assessment with the aim of determining whether consuming fruit, plant shoots and extracts from *Tribulus terrestris* in food supplements is safe, concluding that there is insufficient toxicological data to assess how safe using parts from the *Tribulus terrestris* plant in food supplements is.

In any case, the maximum daily quantity of *Tribulus terrestris* in food supplements should not exceed the dose used for pharmacological purposes. The part of the plant used, whether it was extracted or prepared in some other way, as well as its saponin content, should all be made clear on the supplement itself.

Keywords

Tribulus terrestris, food supplements, saponins.

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1. Introduction

Tribulus terrestris L. (common names: caltrop, goathead, rosette and tribule) is a plant from the Zygophyllaceae family whose use in food supplements is authorised in various European Union countries.

It is an herbaceous perennial plant, which is found naturally in the Mediterranean region although it can be found all around the world. This plant naturally contains various active substances (β-carboline alkaloids and steroidal saponins). Its fruits, leaves and young sprouts are utilised.

Its use in food supplements is authorised in some European Union member states, such as Italy, without any comments or restrictions. However, certain restrictions do exist in other countries. For instance, its use is authorised in Belgium as long as no toxicity is found in regards to the daily recommended dose (Belgium, 2001). In Germany, reference is made to the dose established by the WHO (World Health Organisation) (BVL, 2014), and in France it is required that the parts of the plant be boiled (France, 2014).

In a recent assessment of food supplements containing this plant conducted by Denmark Technical University (DTU), it was concluded that *Tribulus terrestris* can cause serious toxic effects on animals' livers and central nervous systems and that, after having assessed several supplements containing different doses of the plant (2 000-2 250 mg/day), a safe limit intake level cannot be determined.

Thus, in Denmark it is considered that, according to available information, it is not possible to establish a threshold below which use of *Tribulus terrestris* plant parts in food supplements is considered safe for health. Supplements containing said plant are thus classified as non-authorised products, thereby prohibiting its placing on the market. This is reported to the European Rapid Alert System for Food and Feed (RASFF).

In view of the possible side effects attributed to this plant, the Management Board of the Spanish Agency for Consumer Affairs, Food Safety and Nutrition (AECOSAN) has requested that the Section of Food Safety and Nutrition of the Scientific Committee conduct a risk assessment in order to determine whether or not the consumption of fruits, aerial parts and the extracts of *Tribulus terrestris* in food supplements is safe.

2. Characteristics and composition

Tribulus terrestris L. (Zygophyllaceae) is an herbaceous perennial plant found naturally in the Mediterranean region, although nowadays it can be found all over the world. The aerial parts are what are primarily used: fruits, leaves and young plant sprouts.

In its natural form, this plant contains various active substances among which stand out:

- Steroidal saponins (protodioscin, prototribestine, pseudo-protodioscine, dioscine, tribulosaponins A and B, tribestine, tribulosin and terrestrosins A-K): between 2.9 % and 0.0015 % (Kostova and Dinchev, 2005) (DTU, 2014).
- β-Carboline alkaloids (harman, norharman and others): 40-80 mg/kg dry weight (0.004-0.008 %) (EFSA, 2012).

- Flavonoids (kaempferol, quercetin and rutin).
- Lignanamides (tribulusamide A and B).

The content of some of these substances (for example saponins and flavonoids) varies depending on where they originated, the part of the plant and their degree of development (Dinchev et al., 2008).

3. Previous knowledge regarding pharmacological activity and current uses

There are different scientific experimental studies regarding the possible pharmacological activities of *Tribulus terrestris* (WHO, 2009).

In Chinese medicine, it has been used as a treatment for coronary heart disease and was originally used as a diuretic. Nowadays it has fallen into disuse due to different clinical observations associating *Tribulus terrestris* intake with cases of neuronal, hepatic and renal toxicity. It is especially contraindicated for pregnant and breastfeeding women, children and patients with liver or kidney diseases. Its recent comeback is due to a supposed aphrodisiac effect, which has won it the name "herbal viagra".

In the Framework of the Regulation (EC) No 1924/2006 of 20 December 2006 concerning nutrition and health claims made on foods, twelve statements about the health properties associated with *Tribulus terrestris'* fruits and fruit extracts were presented to the European Food Safety Authority (EFSA) for evaluation. The EFSA (2010a,b) has already evaluated and rejected three of these statements and the rest are still pending evaluation.

The applications for evaluation attempted to attribute the different beneficial effects to doses between 0.03 and 0.6 g/powder per day, 0.015 and 0.3 g/day of the aqueous powder extract, 0.5 and 3 g/fruit per day and between 200 and 280 mg of the fruit extract (used as a part of multibotanical combination) (EFSA, 2010a,b).

Its use in food supplements is authorised in some European Union member states, such as Italy, without any comments or restrictions. In this country, it is indicated as a tonic and metabolic support (for mental and physical fatigue) as well as for improved digestive and urinary functioning (Italy, 2014). However, certain restrictions do exist in other countries. For instance, its use is authorised in Belgium as long as no toxicity is found in the daily recommended dose (Belgium, 2001) and in Germany reference is made to the dose defined by the WHO (BVL, 2014). In turn, in France it is required that the parts of the plant be boiled (France, 2014).

4. Toxicity

The EFSA (2012) considers *Tribulus terrestris* to be among the plants whose natural compounds may be of concern for human health when used in foods or food supplements. The German government has included it on the B list - a list containing substances requiring restrictions on use in foods (BVL, 2014).

Tribulus terrestris' toxicity to animals has been widely documented throughout its history as a medicinal plant (McDonough et al., 1994) (Aslani et al., 2003) (Bourke, 2006) (Schmidt et al., 2011)

(Bourke, 2012), and has been reported to have negative neuronal, muscular, hepatic and renal effects such as neuromuscular ataxia, motor impairments, cholestasis, bile duct degradation and inflammation among other effects.

When used as feed in small ruminants (especially in herds of sheep) its use was attributed to two diseases:

- "Geeldikkop", tribulosis ovis or "Yellow big head" (with cases primarily in South Africa, Iran, Australia and the United States). It is a photosensitivity characterised by an accumulation of phylloerythrin (a porphyrin derived from the breakdown of chlorophyll in the rumen) due to a bile duct blockage caused by the crystalline material resulting from the calcium salts of epismilagenin and episarsasapogenin glucuronides. These compounds are diosgenin and yamogenin metabolites, *Tribulus terrestris* steroidal saponins Furthermore, the content and composition of *Tribulus terrestris* saponins can be different based on previous identification of both lithogenic and non-lithogenic groups (Aslani et al., 2003).
- A motor neuron disease causing lower limb weakness which gives rise to tremors, postural asymmetry (bent posture), atrophy in extensor muscles, etc. (Bourke, 2006). The levels of dopamine in the striatum decrease (Bourke, 1987). These effects have been associated with β-carboline alkaloids found in *Tribulus terrestris,* harman and norharman (Bourke et al., 1992). Although their presence is apparently trivial for an acute toxicity, it has been proven that they both accumulate in the central nervous system, irreversibly interacting with specific genes. The doses established as toxic are those equivalents to 54 mg/kg for isolated alkaloids and 44.0 mg/kg for alkaloid-enriched fractions. Other studies indicate that the combination of xanthosine intake (a neuromodulator present in *Tribulus terrestris)* with a molydbenum deficiency could be the cause of this disorder (Bourke, 2012).

In regards to the doses tested during the animal toxicity studies, there is a wide variety with an average of 50 mg/kg (hydroethanol extract) for 8 weeks.

In rats, Paula-Lopes et al. (2006) observed toxic effects to the liver and kidney as well as a decrease in body weight following a daily intake of 5 mg of *Tribulus terrestris* (seeds and fruits) for 60 days. Heidari et al. (2007) indicated unspecified toxic effects in mice following intraperitoneal administration of 400 and 800 mg/kg of a dry methanolic extract obtained from 50 g of the plant.

Jameel et al. (2004) described a case of gynecomastia in a young person, which resulted from the ingestion of a *Tribulus terrestris* preparation used as an alternative to anabolic steroids. Talasaz et al. (2010) described several toxic effects in a young adult resulting from the intake of *Tribulus terrestris* infusions for 2 days. Of particular relevance was the hepatotoxicity, nephrotoxicity and neurotoxicity, although fortunately the effects were reversible once intake was discontinued. Recently, Ryan et al. (2015) confirmed the nephrotoxicity secondary to cholestasis and hyperbilirubinemia from *Tribulus terrestris* in a young patient who took two tablets daily for several months (exact dose and length of time are not indicated). Other recent *in vitro* studies have also indicated cytotoxicity as well as genotoxic and estrogenic activity from *Tribulus terrestris* extracts (Abudayyak et al., 2015).

In a recent assessment of food supplements containing *Tribulus terrestris* that was conducted by Denmark Technical University (DTU), it was reported that *Tribulus terrestris* can cause serious toxic effects on animals' livers and central nervous system. After having assessed several supplements containing different doses of the plant (2 000-2 250 mg/day), a safe limit intake level cannot be determined (DTU, 2014).

Monographs from the Spanish Society of Phytotherapy (SEFIT, 2015) and the World Health Organisation (WHO, 2009) warn against the potential dangers of this plant species.

Exposure assessment

In a sampling of the *Tribulus terrestris* food supplements notified in Spain, it was observed that the content of the *Tribulus terrestris* extract oscillated between 250 and 1 500 mg. The study was performed by selecting food supplements, which referred to the presence of *Tribulus terrestris* in its commercial name and corresponded to its extracts (without specifying the part of the plant). Considering the recommended maximum daily intake of the plant, its consumption would range from 250 to 9 000 mg.

In their monograph discussing *Tribulus terrestris* as a medicinal product, the WHO (2009) established a dosage ranging between 3 and 6 g of the dry powdered fruit (single dose with decoction) or an intake ranging between 6 and 9 g spread out over several doses (with decoction) over the course of the day. In addition, the WHO does not recommend intake in children under 12 years of age given the lack of safety information regarding said plant.

Conclusions of the Scientific Committee

The Scientific Committee concludes that there is not enough toxicological data available to assess the safety of the use of *Tribulus terrestris* plant parts in food supplements.

In any case, the maximum daily quantity of *Tribulus terrestris* in food supplements should not exceed the dose used for pharmacological purposes. The part of the plant used, whether it was extracted or prepared in some other way, as well as its saponin content should all be made clear on the supplement itself.

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