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Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Paullinia cupana* Kunth ex H.B.K. var. *sorbilis* (Mart.) Ducke, semen

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Paullinia cupana</i> Kunth ex H.B.K. var. <i>sorbilis</i> (Mart.) Ducke, semen
Herbal preparation(s)	Powdered herbal substance
Pharmaceutical form(s)	Herbal preparations in solid dosage forms for oral use.
Rapporteur	
Assessor(s)	



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# 1. Introduction

## 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

The herbal substance, *Paulliniae semen* (guarana seed), consists of the entire seeds of *Paullinia cupana* Kunth ex H.B.K. var. *sorbilis* (Mart.) Ducke (= *P. sorbilis* C. Mart.), rapidly dried with heat. It contains not less than 3.5% of caffeine calculated with reference to the dried drug. The material complies with the monograph of the Pharmacopée Française 'Guarana (Graine de)- *Paulliniae sorbilis semen*' [1997].

Other names: Guarana (graine de), Guaraná, Guaranasamen, Guarana Seed [Smith & Atroch 2010].

The Pharmacopée Française contains another monograph 'Guarana (Pâte de)- *Paulliniae sorbilis contriti siccaticque nuclei*' [1997], i.e. Guarana paste, corresponding to the following definition: 'Guarana paste consists of the dried paste obtained from the seed kernels of *Paullinia cupana* Kunth ex H.B.K. var. *sorbilis* (Mart.) Ducke (= *P. sorbilis* C. Mart.) by pounding the material, moistening it and then rapidly drying it with heat. It contains not less than 3% of caffeine calculated with reference to the dried drug'. This Ph. Fr. monograph also states that the dried paste is in the form of cylindrical bars of varying size up to a weight of 300 g and light to dark brown in colour.

Chemical constituents according to existing references [Younggen H. 1943; Steineger & Haensel 1963; Stahl E. 1970; Paris & Moyse 1967; Duke 1985, Gruenwald *et al.* 2007; ESCOP 2009].

- caffeine (1.1-5.8%), and other methylxanthines such as theobromine (0.01-0.17%) and theophylline (0.006-0.25%) [Baumann *et al.* 1995; Pagliarussi *et al.* 2002; Saldana *et al.* 2002];
- tannins (9.5-16% mainly proanthocyanidins), catechin (1.3-6%) and epicatechin (1.2-3.8%) [ESCOP 2009; Gruenwald *et al.* 2007];
- fatty oil (2.2-3.7%) containing acylglycerols (composed mainly of oleic and *cis*-vaccenic acids) and cyanolipids (mainly *cis*-11-eicosenoic and *cis*-vaxenic acids esterified to the nitrile moiety, 2,4-dihydroxy-3-methylene-butyronitrile) [Avato *et al.* 2003; ESCOP 2009; Gruenwald *et al.* 2007];
- a volatile fraction (0.4% v/m) consisting mainly of carvacrol [ESCOP 2009];
- saponins;
- starch (30%);
- proteins (15%).

- Herbal preparation(s)

The Community herbal monograph covers the powdered herbal substance.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

There are combinations, which are registered in the European Union (EU).

This monograph refers only to guarana seed/*Paulliniae semen*.

## 1.2. Information about products on the market in the Member States

### Regulatory status overview

Member State	Regulatory Status				Comments
Austria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
Czech Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
France	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Powdered seeds in caps since 1985, TU
Germany	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Powdered seeds in caps, since 1995 (WEU)
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
Poland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
Spain	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Powdered seeds in caps, since 1984 (TU)
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No prod on the market

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

Other: If known, it should be specified or otherwise add 'Not Known'

This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

### **1.3. Search and assessment methodology**

Search terms: *Paullinia cupana* Kunth ex H.B.K. var. *sorbilis* (Mart.) Ducke (= *P. sorbilis* C. Mart.)  
Guarana seeds, *Paullinia sorbilis*, Paulliniae semen

Databases: Pubmed, Medline, HealLink, Scopus.

Libraries: University of Athens, Laboratory of Pharmacognosy and Chemistry of Natural Products of the University of Athens.

## **2. Historical data on medicinal use**

### **2.1. Information on period of medicinal use in the Community**

The *Paullinia cupana* plant is a woody, evergreen perennial vine up to 10 m long, which climbs through the jungle, native to Amazonian rain forests and cultivated mainly between Manaus and Manau in Brazil.

The medicinal parts of the plant are the peeled, dried, roasted and pulverised seeds, usually formed into a thick paste with water [Gruenwald *et al.* 2007; Smith & Atroch 2010].

The usually unisexual flowers are inconspicuous, yellow to whitish and fragrant. They are in 30 long penicles which only produce female or male flowers at any one time. The fruit is a hazelnut-sized, deep yellow to red-orange, trisectioned capsule, which bursts open when ripe and releases one purple-brown to black seed in a cuplike aril. The leaves of the plant are large palmate, coriaceous, distinctly ribbed and roughly crenate-serrate.

Entire guarana seed, including the testa, is utilised in much of the modern industrial processing (e.g. in the production of extracts) and is the material used in most of the research summarised in this document. In a few papers, it is not clear whether entire seed or material from only the kernels has been used.

Guarana seeds are the seeds of *Paullinia cupana*. A preparation is also made from the ground seeds. Over a period of approximately 75 days, the pollinated flower develops a "ripe" Guarana raceme, which is harvested by hand from October to December. Seed (up to 80 per raceme) are taken out of capsule shells, soaked for a time in water and then finally separated from arillus. Subsequent to being dried in the sun, the seeds are roasted for 2-3 hours in special clay ovens. After being cooled the parchment-like shell is removed and the seeds are ground down. The resulting paste is then smoked over aromatic charcoal. The final product is dark brown in color and in stick form [Gruenwald *et al.* 2007].

#### **Herbal use**

Guarana seeds have played an important role in South American culture and in Amazonian Indian society. It is often taken during periods of fasting to suppress the appetite. In certain regions, the extract is believed to serve as an aphrodisiac and as protection from malaria and dysentery. In the 19<sup>th</sup> century, guarana became popular as a stimulating drink in France [Paris & Moyse 1967] and in 1889 it was introduced as an official drug in the United States Pharmacopoeia where it remained till 1910. Natural diet aids, which rely on daily doses of guarana, have been advertised in the lay press. Guarana is occasionally combined with glucomannan in natural weight loss tablets [Review of Natural Products 2005].

It has been proposed to possess tonic activity [Paris & Moyse 1967] as well as analgesic, anorectic, anti-aggregant, anti-inflammatory, aphrodisiac, astringent, bronchorelaxant, cardiogenic, diuretic, gastrostimulant, immunostimulant, thermogenic and tonic activities [Duke 1985].

In France both the seed and paste of guarana may claim three indications (orally):

- 1) traditionally used to treat mild diarrhoea
- 2) traditionally used to treat functional asthenia
- 3) traditionally used as adjunctive treatment in weight loss programmes (orally, topically) [Bruneton 1999].

In South America, guarana seeds are used to prepare carbonated and flavoured beverages whose concentrations in caffeine is adjusted by adding guarana extracts. The local industry prepares extracts by lixiviation of the seeds, mechanically hulled and sometimes roasted. In recent years, non-alcoholic beverages containing guarana seed have appeared in France [Bruneton 1999].

The stems, leaves and roots of *Paullinia cupana* are used as a fish-killing drug in Central and South America [Review of Natural Products 2005].

A period of 28 years of medicinal use in the EU (see section 2.2.) is complemented by bibliographical evidence on the traditional use for over 30 years on the American continent. *Guarana seeds powder* is well known for its use since 1943 in USA and in Brazil [Youngken 1943]. Thus the requirement of Directive 2004/24/EC for at least 30 years of medicinal use, including at least 15 years in the EU, is fulfilled.

## **2.2. Information on traditional/current indications and specified substances/preparations**

The medical uses of guarana roots and seeds have long been acknowledged, mainly as a stimulant and in nervous headaches [Youngken 1943], as well as for the preparation of a refreshment potion [Stahl 1975]; they were also known to possess antidiarrhoeic and antineuralgic activity [Paris & Moyse 1967].

According to the overview of the European market, there are no herbal preparations containing guarana seed (powder) in the EU for a period of 30 years, however data on the uses in the Member States are complemented by information in literature references; such uses go back to over 30 years [Youngken 1943; Steineger & Haendel 1963; Paris & Moyse 1967; Stahl 1970; Duke 1985; Blumenthal *et al.* 1998; Gruenwald *et al.* 2007; ESCOP 2009].

### **Information on uses in France**

*Information on traditional use since 1985*

Preparations: Powdered seeds (oral use)

Indications:

- 'Traditionally used in functional asthenia'
- 'Traditionally used as an adjuvant to slimming diets'

### **Information on uses in Spain**

*Information on traditional use since 1984*

Preparations: Powdered seeds (oral use)

Indications: 'Traditional herbal medicinal product used in states of general tiredness and convalescence and as an adjuvant in slimming diets. Based upon long-standing use'.

*Information on traditional use according to Directive 2004/24/EC*

THMP containing *Paullinia cupana* Kunth, semen registered according to Directive 2004/24/EC on 31 May 2011 in the following indication:

Indication: 'THMP used for symptoms of fatigue and sensation of weakness, convalescence, and as an aid in slimming diets. Indications exclusively based on long-standing use.'

**Information on uses in Germany**

*Information of well-established use since 1995*

Preparations: Powdered seeds (oral use)

Indications: 'For the short-term treatment of physical fatigue'.

Contraindications: Guarana seed should not be taken by patients with hypersensitivity to guarana seed, rhythm disturbances of the heart such as accelerated or irregular heart beat (risk of reinforcement), liver cirrhosis (risk of accumulation of caffeine), hyperthyroidism (risk of reinforcing the caffeine side effects), anxiety disorders (risk of reinforcement), gastric or duodenal ulcers, and by children under 12 years.

Warnings and precautions for use: The drug contains caffeine. The chronic use of caffeine, especially at larger doses, can lead to the development of tolerance and side effects. Abrupt discontinuation after longtime consuming of higher doses can cause headache, fatigue, muscular pain, nervousness and vegetative symptoms.

Effects on ability to drive and use machines are not known. The drug cannot compensate decrease in functional capacity. Functional capacity decrease caused by alcohol cannot be compensated.

In individual cases alcohol is absorbed by the organism even faster.

Interactions with other drugs and other forms of interaction: The caffeine contained in guarana drugs may decrease the sedative effects of numerous substances such as hypnotics. It increases the effects of pressor drugs and thyroid medication. For substances with a broad spectrum of activity (benzodiazepines), interactions may vary and may not be predictable. The caffeine contained in guarana increases the analgesic effect of paracetamol and aspirin. Oral contraceptives (birth-control pills), cimetidine, disulfiram reduce the degradation of caffeine in the liver. Hypnotics (barbiturates) and smoking accelerate the degradation of caffeine. The elimination of theophylline is decreased by caffeine. The concomitant administration of gyrase inhibitors (antibiotics) of the quinolone-carbonic-acid type may delay the elimination of caffeine and its degradation product paraxanthine. The drug increases the dependence potential of substances of the ephedrine type.

*Conclusion*

Evidence of long-standing use as defined in the provisions of Directive 2004/24/EC is available: traditional medicinal use is confirmed by uses in the Member States and a large number of publications providing consistent information.

The indication found in the draft Community herbal monograph is the following:

'Traditional herbal medicinal product for symptoms of fatigue and sensation of weakness'.

### **2.3. Specified strength/posology/route of administration/duration of use for relevant preparations and indications**

#### **Information on posology in France**

*Information on traditional use since 1985*

Preparations: Powdered seeds

Pharmaceutical form: Hard capsules

Posology for oral use in adults: 3-5 times daily (containing 445 mg powder each)

#### **Information on posology in Spain**

*Information on traditional use since 1984*

Preparations: Powdered seeds

Pharmaceutical form: Hard capsules

Posology for oral use in adults: 3-5 times daily (containing 340 mg powder each), up to 2040 mg/day

*Information on traditional use according to Directive 2004/24/EC*

THMP registered on 31 May 2011 with the following posology:

*Paullinia cupana* Kunth, semen (340 mg per capsule) with a recommended posology of 3 capsules 2 times a day

#### **Information on posology in Germany**

*Information of well-established use since 1995*

Preparations: Powdered seeds

Pharmaceutical form: Hard capsules

Posology for oral use in adults: daily 2 capsules containing 500 mg; an increase up to 3 times daily 2 capsules is possible.

#### *Conclusion*

Based on literature data and information from the Member States, the following posology and duration of use are found in the draft Community herbal monograph:

#### **Posology**

*Adults and Elderly*

Powdered herbal substance

Single dose: 450 mg, up to 2,250 mg/day.

#### **Duration of use**

If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

## 3. Non-Clinical Data

### 3.1 Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

#### *In vitro* experiments

##### Antimicrobial activity

An ethanolic dry extract of guarana seed (6.7:1) exhibited antibacterial activity against Gram-negative bacteria with minimal inhibitory concentrations (MICs) of 16 µg/ml for *Pseudomonas aeruginosa* and 32 µg/ml for *Escherichia coli*, *Proteus vulgaris* and *P. mirabilis*, and against Gram-positive bacteria (*Staphylococcus aureus* and *S. epidermidis*) with MICs of 64 and 128 µg/ml respectively. *Bacillus subtilis* and *Streptococcus faecalis* were not inhibited [Basile *et al.* 2005].

In contrast, even at concentrations up to 1000 µg/ml, a crude lyophilized extract of guarana seed and semi-purified fractions from it did not exhibit activity against *S. aureus*, *B. subtilis*, *E. coli* or *P. aeruginosa* [ESCOP 2009].

The guarana seed extracts (water, methanol, 35% acetone and 60% ethanol) were tested against three food-borne fungi: *Aspergillus niger*, *Trichoderma viride* and *Penicillium cyclopium*, and three health-damaging bacteria: *Escherichia coli*, *Pseudomonas fluorescens* and *Bacillus cereus* by the agar well diffusion and broth dilution assay. The alcoholic guarana seed extracts displayed stronger antimicrobial activity against all tested microorganisms than did water extracts. The authors concluded that the results presented may suggest that seed extracts of *Paullinia cupana* possess strong antimicrobial properties, and they can therefore be used as a natural additive in food, cosmetic and pharmaceutical industries [Majhenič *et al.* 2007].

*In vitro* assessment of the antibacterial potential of the *Paullinia cupana* extracts (the aqueous and crude extracts as well as semi-purified fractions) against *Streptococcus mutans* showed that these could be used in the prevention of bacterial dental plaque [Yamaguti-Sasaki *et al.* 2007].

##### Antioxidant activity

After treatment of 3T3-L1 cells with ferric ammonium citrate, 2 µg/ml of an ethanolic dry extract of guarana seed (6.7:1; corresponding to 0.012 µg/ml of catechin) reduced lipid peroxidation by 65.2% as measured in the malonyldialdehyde test [ESCOP 2009; Basile *et al.* 2005].

A lyophilized ethanolic (50% V/V) extract of guarana seed inhibited lipid peroxidation in rat brain homogenates in a concentration-dependent manner with IC<sub>50</sub> of 1.2 µg/ml [Mattei *et al.* 1998].

The antioxidant and antibacterial activities of *Paullinia cupana* were detected. The seeds were extracted with water, methanol, 35% acetone and 60% ethanol, at room and at boiling temperature of solvent. The antioxidant and radical-scavenging activities of guarana seed extracts were evaluated using the β-carotene-linoleic acid emulsion system and the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH). All tested guarana seed extracts displayed strong antioxidant and radical-scavenging properties [Majhenič *et al.* 2007].

Measurement of the antioxidant activity by reduction of the DPPH radical confirmed the anti-radical properties of the aqueous and crude extracts and semi-purified fractions. The EPA fraction showed radical-scavenging activity (RSA) and protected DPPH from discoloration at 5.23±0.08 µg/ml (RSD%=1.49), and for the phosphomolybdenum complex showed a higher Relative Antioxidant Capacity (RAC) at 0.75±0.01 µg/ml (1.75) [Yamaguti-Sasaki *et al.* 2007].

## **Anticoagulant activity**

An aqueous extract corresponding to 5 mg of guarana seed, and the polar and xanthine fractions from it, decreased platelet aggregation induced by ADP in platelet-rich rabbit plasma by 37, 27 and 31% ( $p < 0.05$ ) and platelet thromboxane formation from [ $^{14}\text{C}$ ]-arachidonic acid by 78, 70 and 50% ( $p < 0.05$ ) respectively, compared to controls [ESCOP 2009].

An aqueous extract from guarana seed (1 part to 10 of water) and its xanthine fractions inhibited platelet aggregation induced by ADP or arachidonic acid in both human and rabbit platelet-rich plasma in a dose-dependent manner [ESCOP 2009].

## **Other effects**

A significant decrease from 98% to 36% in the uptake of radioactivity (technetium-99m) by red blood cells from rats was observed in the presence of an aqueous (saline) extract from guarana seed powder ( $p < 0.05$ ). Comparison of the shape of the red blood cells before and after treatment with the guarana seed extract revealed important morphological changes, which could explain the decrease in uptake of technetium-99m [de Oliveira *et al.* 2002].

## ***In vivo* experiments**

### **Bioactivities from guarana seed**

#### **Antimutagenic activity**

BALB/c female mice were pretreated with an extract of guarana seed (containing 13% of total tannins, including approximately 6% of condensed tannins) by gavage at 2 mg/g body weight daily for 16 days. They then received an intraperitoneal dose of N-nitrosodiethylamine (DEN) at 160  $\mu\text{g/g}$  to induce DNA damage. Other groups received water, guarana seed at 2 mg/g or DEN at 160  $\mu\text{g/g}$ . Extensive degeneration of the liver characterised by hepatocyte swelling and cytoplasmic vacuolisation, was observed in DEN and DEN+guarana groups, whereas control groups presented no histological difference after 4 hours. In the comet assay, a measure of DNA damage in the liver, pre-treatment of mice with guarana seed reduced the image length by 52.5% ( $p < 0.05$ ). These results were reinforced by data from tests using the DNA smear fragmentation technique: DNA damage was not observed in treated and guarana seed-treated animals, while the DEN group showed more extensive DNA damage than the DEN+guarana group [Fukumasu *et al.* 2006; Gruenwald *et al.* 2007].

#### **Anticoagulant effects**

Administration of a solution of a guarana seed aqueous extract (10%, 1 ml intravenously or 20 ml nasogastrically) induced a marked decrease in rabbit platelet aggregation in response to ADP ( $p < 0.02$ ) or arachidonate ( $p < 0.01$ ) [ESCOP 2009].

#### **Cytoprotective and antiproliferative effects**

BALB/c mice pre-treated intraperitoneally with DEN at 10  $\mu\text{g/g}$  body weight received ad libitum powdered guarana seed added to food at 0.1, 1 and 2 mg/g, or the commercial food only, for 25 weeks. Compared to controls, the highest dose of guarana seed caused a significant reduction in the multiplicity of gross lesions ( $p < 0.05$ ) and a 50% decrease in lesion incidence ( $p = 0.0325$ ) in the liver. The same dose significantly reduced the number of preneoplastic lesions in basophilic cells ( $p < 0.05$ ) and also reduced proliferating cell nuclear antigen expression ( $p < 0.05$ ) [Fukumasu *et al.* 2006].

Gastric mucosal haemorrhagic erosions in rats (induced by 1 ml of ethanol) were significantly reduced by a guarana seed dry extract administered orally at 50 mg/kg ( $p < 0.01$ ) and 100 mg/kg ( $p < 0.05$ ) and by caffeine at 20 mg/kg ( $p < 0.05$ ) and 30 mg/kg ( $p < 0.01$ ). In indometacin-induced gastric mucosal damage, the guarana seed extract at 100 mg/kg significantly reduced the ulcer score to 26.5 compared to 47.5 in the control group ( $p < 0.01$ ), while caffeine had no effect. In 4-hour pylorus-ligated rats, guarana seed and caffeine administered intraduodenally at the same dose level reduced total gastric acid output and gastric juice volume in a dose-dependent manner. Gastrointestinal transit was not significantly modified by these agents [Campos *et al.* 2003].

One hour after oral administration of a maltose solution to mice at 2 g/kg body weight oral administration of an aqueous guarana seed dry extract (4:1) at 500 mg/kg increased blood glucose levels ( $p < 0.01$ ) and decreased liver glycogen content ( $p < 0.05$ ) compared to controls. The same dose significantly suppressed exercise-induced hypoglycaemia ( $p < 0.05$  at 60 min), but did not affect blood glucose levels in adrenaline-induced glycogenolytic effect in mice or exercising mice [Miura *et al.* 1998].

The antiproliferative effect of *Paullinia cupana* treatment in Ehrlich Ascites Carcinoma (EAC)-bearing animals was studied. Female mice were treated with 3 doses of powdered *Paullinia cupana* (100, 1000 and 2000 mg/kg) for 7 days, injected with 105 EAC cells and treated up to day 21. In addition, a survival experiment was carried out with the same protocol. *Paullinia cupana* decreased the ascites volume ( $p = 0.0120$ ), cell number ( $p = 0.0004$ ) and haemorrhage ( $p = 0.0054$ ). This occurred through a G1-phase arrest ( $p < 0.01$ ) induced by a decreased gene expression of Cyclin D1 in EAC cells. Furthermore, *Paullinia cupana* significantly increased the survival of EAC-bearing animals ( $p = 0.0012$ ). In conclusion, the *Paullinia cupana* growth control effect in this model was correlated with a decreased expression of Cyclin D1 and a G1-phase arrest. The authors concluded that these results reinforce the cancer therapeutic potential of the plant [Fukumasu *et al.* 2011].

### Stimulant effects

A guarana seed extract administered orally to mice at 25 and 50 mg/kg body weight one hour before a forced swimming test (FST) significantly reduced the duration of immobility during a 6 min period ( $p < 0.001$  and  $p < 0.05$  respectively), suggesting an antidepressant-like effect. A similar effect was seen with caffeine at 10 and 20 mg/kg ( $p < 0.01$ ). High doses of this extract (100 mg/kg) and caffeine (30 mg/kg) failed to produce antidepressant-like or antistressor activity but significantly enhanced locomotor activity ( $p < 0.05$ ) in the open-field test. The effects of the extract (50 mg/kg) and caffeine (20 mg/kg) on swimming-induced immobility were also investigated in mice orally pretreated with 0.1 mg/kg of cyclopentyladenosine (CPA), an adenosine antagonist. Only caffeine significantly blocked the CPA effect ( $p < 0.001$ ), suggesting that mechanism(s) other than the adenosinergic mechanism are involved in the antidepressant-like activity of guarana [Campos *et al.* 2005].

A suspension of guarana seed powder (16% of tannins, 2.1% of caffeine), given at a concentration of 0.3 mg/ml as the only source of liquid, produced significant increases in the physical capacity of mice subjected to forced swimming tests after 100 and 200 days of treatment ( $p < 0.05$ ). Guarana seed powder, after both single intraperitoneal administration (0.3 and 30 mg/kg body weight) and chronic oral administration at 0.3 mg/ml for 9 months, reversed the amnesic effect of scopolamine in a passive avoidance test in mice and rats. Learning in rats treated chronically with guarana seed powder (0.3 and 30 mg/ml) and evaluated in active avoidance tests did not show significant alterations after 75 nor 120 days compared to controls. In the Lashly III maze test, chronic oral administration of guarana seed (0.3 and 30 g/ml) or caffeine (0.1 mg/ml) as the only source of liquid for one year caused no difference in performance of these animals with regard to time and the number of mistakes when compared to controls [Espinola *et al.* 1997].

## Cognitive effects

Various doses of a crude lyophilized extract of guarana seed (EBPC) and semi-purified fractions from it (EPA and EPB) given orally, and of caffeine given intraperitoneally, were administered to rats once daily for 40 days. The rats also received either scopolamine at 2 mg/kg or a sodium chloride solution intraperitoneally 30 min before the Morris Water Maze Test (MWM). EBPC (30 mg/kg) and EPA (2 mg/kg) but not EPB (2 and 4 mg/kg) significantly reduced the escape latency in normal rats ( $p < 0.05$ ) and in scopolamine amnesic rats compared to controls. In the Open-Field Test (OFT) EBPC at 30 mg/kg and EPA or EPB at 2 and 4 mg/kg did not alter the number of crossings, whereas caffeine at 10 mg/kg significantly increased the number of crossings compared to the control ( $p < 0.05$ ) [ESCOP 2009].

In another experiment acute oral administration of EBPC (3, 30 and 60 mg/kg), EPA (2 and 4 mg/kg) or EPB (2 and 4 mg/kg) to rats did not affect parameters analysed in the Plus Maze Test (PMT), FST or OFT. EBPC (3, 30 and 60 mg/kg) administered orally to rats for 40 days did not show anxiolytic activity. Oral administration of EBPC (30 mg/kg) or EPA (4 mg/kg), or intraperitoneal administration of caffeine (10 mg/kg) or imipramine (20 mg/kg) for 40 days significantly decreased immobility time in the FST ( $p < 0.01$ ) compared to controls (saline + 2% Tween 80). Only caffeine increased locomotor activity in the OFT ( $p < 0.05$ ). EPB (2 and 4 mg/kg) did not alter immobility time in the FST or locomotor activity in the OFT. These results suggested that components other than caffeine are responsible for the antidepressant effect observed with EPBC and EPA [Otobone *et al.* 2007].

In another recent study [Roncon *et al.* 2011] the effects of chronic administration of a semi-purified extract (Purified Extract A - PEA; 4, 8, or 16 mg/kg) of *Paullinia cupana* seeds on rats submitted to the elevated T-maze (ETM) model of generalised anxiety and panic disorders, were studied. The selective serotonin (5-HT) reuptake inhibitor (SSRI) paroxetine (PAR; 3 mg/kg), was used as a positive control. To evaluate possible serotonergic and dopaminergic neurotransmission involvement in the action of PEA during the ETM test, ineffective doses of metergoline (MET; 5-HT<sub>2A/2C</sub> antagonist receptor) or sulpiride (SUL; dopaminergic receptor antagonist) were acutely administered together with the PEA. The locomotion of the rats was assessed in a circular arena following each drug treatment. Both PEA (8 and 16 mg/kg) and PAR (3 mg/kg) increased one-way escape latencies from the open arm of the ETM, indicating a panicolytic effect compared to the control group. MET, in higher doses (1, 2 or 3 mg/kg), produced a panicolytic effect in the ETM test, whereas SUL did not (10, 20 or 40 mg/kg). The panicolytic effect produced by PEA (8 mg/kg) was blocked by both MET (2 mg/kg) and SUL (20 mg/kg), whereas the panicolytic effect produced by PAR (3 mg/kg) was blocked only by MET (2 mg/kg). These results show that chronic treatment with PEA produces a panicolytic effect during the ETM test, and that the dopaminergic and the serotonergic neurotransmission systems are involved in this effect.

## Anti-obesity effects

Effects on body weight, food and water intake, muscle fat content, oleate incorporation, glycogen content and carnitine palmitoyltransferase I (CPT I) activity as well as CPT I mRNA expression were assessed using 2 dose levels (0.130 g/kg and 0.325 g/kg body weight) of a hydroalcoholic dry extract of guarana seed (6:1, 66% V/V; 0.153 g of caffeine per g) and the same extract decaffeinated. These extracts were orally administered daily for 14 days to sedentary and swimming-trained rats. The higher dose of guarana significantly decreased total food intake compared to controls ( $p < 0.05$ ), although the total weight gain was not significantly changed. Both doses of decaffeinated extract induced lower weight gain. Water consumption was unaffected. To evaluate the fat content of, and <sup>14</sup>C-oleate incorporation into, skeletal muscle the animals received intragastrically 0.5 ml of [<sup>14</sup>C]-triolein corresponding to 2.5 µCi. After 5 hours, the neutral lipid content in soleus and gastrocnemius muscles

was not different between the groups whereas muscle oleate incorporation was decreased between in sedentary and trained rats receiving decaffeinated guarana seed extract compared to both doses of guarana seed extract. CPT I mRNA expression in the gastrocnemius of trained rats was significantly reduced by the lower dose of decaffeinated guarana seed extract compared to the same dose of whole extract ( $p < 0.005$ ). In trained rats, guarana seed extract at 0.130 g/kg decreased plasma lactate content compared to the decaffeinated extract and produced higher muscle glycogen content in relation to other groups. The results showed that the guarana seed extract had an effect on aspects of lipid metabolism that was abolished by decaffeination [ESCOP 2009].

### **Other effects**

A hydroethanolic (50% V/V) extract of guarana seed had a vasorelaxant action on intact endothelium rings of rats thoracic aorta ( $EC_{50} = 22.7 \mu\text{g/ml}$ ). A similar effect was observed on rings of rubbed (denuded) endothelium from rat thoracic aorta precontracted with 0.1  $\mu\text{M}$  noradrenaline ( $EC_{50} = 233.9 \mu\text{g/ml}$ ) [Callixto *et al.* 1997].

Single bolus injections of a hydroethanolic (50% V/V) dry extract of guarana seed (0.5-5 mg) caused a dose-dependent relaxant effect on the rabbit corpus cavernosum. This effect was not significantly affected by an infusion of  $N^{\omega}$ -nitro-L-arginine methyl ester or by a guanylate cyclase inhibitor, 1H-[1,2,4]-oxadiazolo [4,3-*al*]quinoxalin-1-one, both at a concentration of 10  $\mu\text{M}$ . Incubations of rabbit corpus cavernosum homogenates with the guarana extract at 1, 10 and 100 mg/ml for 5 min increased cAMP levels by 200, 150 and 89% respectively [Antunes *et al.* 2001].

The influence of a commercial extract of *Paullinia cupana* seeds (guarana) on the binding of technetium-99m-dimercaptosuccinic acid ( $^{99\text{m}}\text{Tc-DMSA}$ ) on blood constituents was studied. Plasma (P) and blood cells (BC) from Wistar rats (control and treated) were separated. P and BC were precipitated with trichloroacetic acid (TCA) or ammonium sulphate and soluble and insoluble fractions (IF) isolated. The percentage of incorporated radioactivity (%ATI) in each fraction was determined. The treatment influenced the %ATI in IF-P and in IF-BC isolated by TCA precipitation [Freitas *et al.* 2007].

In a very recent study [Leite *et al.* 2011] *Paullinia cupana*'s potential to attenuate cadmium-induced damages in Wistar rat testis was investigated. Adult male Wistar rats were either pre-treated with 2 mg/g body weight of powdered *Paullinia cupana* seed during 56 days and/or injected with cadmium chloride at a dose of 1.15 mg/kg body weight. After cadmium exposition (48 hours), testes samples were evaluated by histological and stereological analyses. Both groups exposed to cadmium presented evident morphological alterations relative to control animals. A few rodents showed massive cell death in the seminiferous epithelium and intertubular space, indicating that some animals are more sensitive to cadmium. Despite the alterations observed in both groups, pre-treatment with *Paullinia cupana* was effective in attenuating morphological changes in Leydig cells, as well as reducing inflammatory response, relative to animals exclusively exposed to the metal. Animals treated only with *Paullinia cupana* presented a significant increase in plasma testosterone levels and a significant increase in volumetric proportions of seminiferous tubules, which are indicative of spermatogenic stimulation.

### **3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof**

No data on guarana seed powder have been found or reported.

### **3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof**

#### **Single-dose and repeated-dose toxicity studies**

When given as the only source of liquid for 60 days neither aqueous suspensions of guarana seed powder at concentrations of 0.3 and 3 mg/ml nor caffeine at 0.1 mg/ml altered pentobarbital-induced sleeping time in 6-month old male mice. The body weight of 10-month old male rats receiving these treatments for 12 months did not significantly vary from that of control animals. There was no difference in mortality between treated and control groups of mice or rats for 23 months. When given to mice (6 and 14 months old) and rats (12 months old) for 2 and 12 months respectively, these solutions did not alter locomotor activity. No alterations in heart, lungs, stomach, small and large intestine, liver, pancreas, kidneys, bladder or spleen were observed in 3-month old male mice treated with the 3 mg/ml guarana suspension for 7 months except for a bronchial adenoma in the control [ESCOP 2009].

No changes in body weight or mortality were observed in 3-month old male rats after daily oral administration for 40 days of a crude lyophilized extract of guarana seed at 30 mg/kg, or two semi-purified fractions from it at 2 and 4 mg/kg, or caffeine at 10 mg/kg. No alterations in appearance or weight of heart, liver, spleen or kidneys were evident in these animals compared to controls [ESCOP 2009].

Rats given a suspension of guarana seed powder (16% of tannins, 2.1% of caffeine) at concentrations of 0.3 mg/ml or 30 mg/ml, or caffeine at 0.1 mg/ml, as sole sources of liquid for 23 months had the same average lifespan as a control group [ESCOP 2009].

#### **Acute toxicity**

An aqueous suspension of guarana seed powder administered orally at 2 g/kg and intraperitoneally at 1 and 2 g/kg body weight to 3-month old male mice did not induce any significant changes in urination frequency, defecation, piloerection, motor activity, tremor, convulsion, muscular tonus, posture, loss of reflexes, lacrimation or salivation compared to control groups [ESCOP 2009].

One semi-purified extract (EPA fraction, containing caffeine and several flavan-3-ols and proanthocyanidins) of seeds of *Paullinia cupana* (guaraná) was tested for its toxicity in rodents. Acute toxicity was tested in male Swiss mice, which received different doses orally (OR) and intraperitoneally (ip); control groups received water. These tests produced acute mortality, with LD<sub>50</sub> of 1.825 g/kg (OR) and 0.827 g/kg (ip), and a significant weight decrease in lungs of mice receiving a dose of 0.1 g/kg [Antonelli-Ushirobira *et al.* 2010].

In the repeated-dose toxicity test, the extract was administered orally daily to male and female Wistar rats, at doses of 30, 150, and 300 mg/kg/day for 90 days. Their behaviour, mortality, weight changes, laboratory tests, and the weights and histopathology of organs were evaluated. No rats died during the tests. Males dosed at 150 or 300 mg/kg gained weight more slowly and lost kidney weight (absolute and relative weights) compared to the control group. Haematological and biochemical tests showed few changes, differing somewhat between males and females; the histopathological evaluation indicated no significant changes. These results indicated that the tested extract of *Paullinia* semen (guaraná) caused no toxicity in rats at the smallest dose evaluated (30 mg/kg) [Antonelli-Ushirobira *et al.* 2010].

#### **Genotoxicity studies**

At high concentrations, aqueous extracts of guarana seed powder (extracted at 200 mg per ml; 0.05 to 0.5 ml/plate) and a lyophilized aqueous guarana seed dry extract (30 mg/plate) produced lysogenic

induction in strain WP2s( $\lambda$ ) of *Escherichia coli* B/r. This genotoxic effect was attributed to a molecular complex formed by caffeine and catechin or epicatechin in the presence of potassium [ESCOP 2009].

In the Ames test, the same lyophilized aqueous guarana seed dry extract showed low mutagenic activity at 30 mg/plate with *Salmonella typhimurium* strain TA97, but neither mutagenic nor toxic activity with strains TA98, TA100 and TA102 [ESCOP 2009]. These tests do not fulfill all the requirements of the OECD guideline.

The effects of 4 different concentrations of a guarana seed aqueous extract (10, 20, 30 and 40 mg/ml) were tested on Chinese hamster ovary cells. The extract was not cytotoxic at 10 mg/ml and IC<sub>50</sub> values of 32 mg/ml in the neutral red uptake assay, 39.3 mg/ml in the total protein content assay and 34.6 mg/ml in the tetrazolium assay were lower than the highest concentration tested (i.e. 40 mg/ml). EC<sub>50</sub> values in the microtox assay were 21.4 and 19.1 mg/ml at 5 and 15 min respectively [ESCOP 2009].

### **Carcinogenicity studies**

No data on carcinogenicity of guarana seed can be found in the scientific literature.

### **Reproduction and developmental toxicity studies**

No reproductive and developmental toxicity studies carried out on guarana seed in the scientific literature.

The safety of guarana seeds during pregnancy and lactation has not been established. In accordance with general medical practice, the herbal medicinal products (finished products) should not be used during pregnancy and lactation without medical advice.

## **3.4. Overall conclusions on non-clinical data**

Guarana seeds have been officially recognised at least since 1985 in the EU traditionally as a herbal medicinal product for symptoms of fatigue and sensation of weakness, while this use was widely known in Brazil and USA since at least the 1940's.

The published data referring to the indications and preparations are supported on the basis of existing data on the pharmacological activities [Duke 1985; PDR 2009]; non-clinical data support the proposed traditional use of guarana seeds and preparations thereof in the indication found in the draft monograph.

The lack of adequate genotoxicity, carcinogenicity as well as reproductive and developmental toxicity studies do not allow the establishment of a Community list entry.

## **4. Clinical Data**

### **4.1. Clinical Pharmacology**

#### **4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents**

No data available.

#### **4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents**

To assess the clearance time of xanthines, 20 g of guarana seed powder was administered under the tongue of horses twice a day for 5 consecutive days. After the first administration caffeine was detected in the urine for up to 9 days, and theobromine and theophylline for up to 13 days. No amine metabolites (with possible psychoactive effects) were detected in human urine after oral ingestion of guarana seed powder as 2 times 10 g with 100 ml of water [ESCOP 2009].

No linear association between caffeine consumption and incident hypertension was found. Even though habitual consumption was not associated with an increased risk of hypertension, consumption of caffeinated beverages was associated with it. Further research to elucidate the role of caffeinated beverages in hypertension is warranted [Winkelmayer *et al.* 2005].

### **4.2. Clinical Efficacy**

#### **4.2.1. Dose response studies**

No data available.

#### **4.2.2. Clinical studies (case studies and clinical trials)**

##### **Behavioural effects**

In a randomised, double-blind, placebo-controlled study, volunteers aged 20-35 years received 2 times 500 mg of guarana seed powder containing 21 mg of caffeine and 160 mg of tannins (n=10), daily for 3 days to evaluate acute effects on cognitive function, sleep and anxiety. No significant changes were observed in any of the groups compared to baseline [ESCOP 2009].

In a randomised, double-blind, placebo-controlled study, healthy 60-year old volunteers received 2 times 500 mg of guarana seed powder containing 21 mg of caffeine and 160 mg of tannins (n=15), daily for 150 days to assess effects on cognitive function, sleep and anxiety. The only significant change observed was an improved result in the Mosaic test for visual and spatial organisation in the guarana seed group ( $p < 0.05$ ) [ESCOP 2009].

In a randomised, double-blind, placebo-controlled study, the cognitive and mood effects of a single 75 mg dose of a standardised guarana seed dry extract (3-7:1, ethanol 50% V/V; approximately 12% caffeine) were assessed in 28 undergraduate volunteers. Cognitive performance and subjective mood were assessed pre-dose and at 1, 2.5, 4 and 6 hours post-dose using the Cognitive Drug Research computerised assessment battery, serial subtraction tasks and Bond-Lader mood scales. Performance increased in the speed of attention task and significantly speeded up the sentence verification task ( $p = 0.003$  after 2.5 hours,  $p < 0.05$  after 4 and 6 hours). There were no significant effects on mood [ESCOP 2009].

In a randomised, double-blind, placebo-controlled study, single doses (37.5 mg, 75 mg, 150 mg and 300 mg) of a standardised guarana seed dry extract (3-7:1 ethanol 50% V/V; 11-12% caffeine) and a placebo were administered on separate days to 26 undergraduate volunteers to assess acute mood and cognitive effects. Alertness and contentedness ratings were significantly and dose-dependently enhanced in all verum groups, with the 300 mg dose producing the greatest improvement ( $p = 0.009$ ) [Haskell *et al.* 2007].

## Weight loss

A double-blind, parallel, placebo-controlled trial was conducted in 47 healthy volunteers, aged 20-60, to evaluate the effects of a herbal preparation containing Yerbe Maté, Guarana and Damiana (YGD) on gastric emptying and weight loss. Subjects, who had body weight taken and ultrasound performed, were instructed to fast for 8 hours prior to the study start. They were then given three YGD capsules, each containing 112 mg Yerbe Maté, 95 mg guarana (seeds) and 36 mg Damiana extract, to ingest with 20 ml of apple juice and 15 min later, 400 ml of apple juice. The subjects were evaluated at 10 and 45 days. The mean gastric emptying times were 38 +/- 7.6 min following placebo capsules and 58 +/- 15 min after YGD capsules (a mean of 53% increase). Subjects in the treatment group showed an increased weight loss (mean decrease of 5.1 +/- 0.5 kg after 45 days on YGD vs 0.3 +/- 0.08 kg with placebo). The active treatment was a combination product with each constituent having its own potential to cause weight loss [Andersen 2001].

The effect of a mixture of green tea and guarana seeds extracts containing a fixed dose of caffeine and variable doses of epigallocatechin-3-gallate (EGCG) on 24-hour energy expenditure and fat oxidation was examined. Fourteen subjects took part in this randomised, placebo-controlled, double-blind, cross-over study. Each subject was tested 5 times in a metabolic chamber to measure 24-hour energy expenditure, substrate oxidation and blood pressure. During each stay, the subjects ingested a capsule of placebo or capsules containing 200 mg caffeine and a variable dose of EGCG (90, 200, 300, 400 mg) three times daily, 30 min before standardised meals. Twenty-four hour energy expenditure increased significantly by about 750 kJ with all EGCG-caffeine mixtures compared with placebo. No effect of the EGCG-caffeine mixture was observed on lipid oxidation. Systolic and diastolic blood pressure increased by about 7 and 5 mmHg respectively, with the EGCG-caffeine mixtures compared with placebo. The increase was significant only for 24-hour diastolic blood pressure. The increase in 24-hour energy expenditure with EGCG-caffeine preparation was similar with all doses of EGCG in the mixtures [Bérubé-Parent *et al.* 2005].

## Stimulant effects

In a randomised, single-blind, placebo-controlled study, 15 normal sleepers were treated with 250 ml of a guarana seed drink (500 mg of guarana seed powder in 100 ml) or placebo. Subjective mood scales and a battery of performance tests were assessed as a baseline before sleep. After a night restricted to 4 hours of sleep, the drink was consumed at 7.15 in the morning. Tests were performed at 2-hour intervals. Guarana seed significantly improved critical flicker fusion and hand dynamometer squeeze duration ( $p < 0.05$ ) and produced positive trends on mood [ESCOP 2009].

## Thermogenic effects

In a randomised, double-blind, placebo-controlled study, 12 volunteers (average age 25 years) received 2.72 g of guarana seed powder (4% caffeine) or placebo. After 3 hours, the respiratory quotient (indicating the proportion of fat oxidized) and systolic blood pressure had increased significantly (both  $p < 0.05$ ), but no significant change in energy expenditure was observed [Martinet *et al.* 1999].

## Improvement of fatigue and depression in cancer chemotherapy

The purpose of this study was to evaluate the effectiveness of a guarana (*Paullinia cupana*) standardised dried extract on fatigue, sleep quality, anxiety, depression symptoms, and menopause in a group of breast cancer (BC) chemotherapy patients. Patients and methods: Patients with progressive fatigue after their first cycle of chemotherapy were randomised to receive either guarana 50 mg by mouth twice daily (32 patients) or placebo (43 patients) for 21 days. After a 7-day washout period,

patients were crossed over to the opposite experimental arm. All patients were evaluated on days 1, 21 and 49. The primary endpoint was the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire score, and secondary endpoints were the results of the Functional Assessment of Chronic Illness Therapy-Endocrine Symptoms (FACT-ES), Brief Fatigue Inventory (BFI), Pittsburgh Sleep Quality Index, Chalder Fatigue Scale, and Hospital Anxiety and Depression Scale. Guarana significantly improved the FACIT-F, FACT-ES and BFI global scores compared to placebo on days 21 and 49 ( $p < 0.01$ ). The Chalder Scale improved significantly on day 21 ( $p < 0.01$ ) but not on day 49 ( $p = 0.27$ ). Guarana did not produce any Common Terminology Criteria for Adverse Events grades 2, 3, or 4 toxicities and did not worsen sleep quality or cause anxiety or depression. Conclusions: Guarana is an effective, inexpensive and nontoxic alternative for the short-term treatment of fatigue in BC patients receiving systemic chemotherapy. Further studies are needed to confirm these results and to evaluate their generalisability to chronic cancer-related fatigue and to other types of cancer [de Oliveira Campos *et al.* 2011].

The aim of this randomised, double-blind crossover study was to evaluate the effectiveness of guarana seeds in the treatment of postradiation depression and fatigue. Methods: 36 patients with breast cancer undergoing adjuvant radiation therapy were randomised to receive either guarana 75 mg daily p.o. or placebo. Patients were switched to the other experimental arm at the middle of the radiation treatment, which consisted of 28 daily fractions of 180 cGy. Evaluations were conducted at the beginning, at the middle, and at the end of radiation therapy. Results: The authors were unable to show any statistically significant differences between the guarana and the placebo-treated group with any of the measured scores. Also, within the same group, they did not see any statistically significant associations during either the guarana- or placebo-treated periods with any of the measures [Da Costa Miranda *et al.* 2009].

#### **4.2.3. Clinical studies in special populations (e.g. elderly and children)**

None reported.

#### **4.3. Overall conclusions on clinical pharmacology and efficacy**

There are several recent clinical studies in published literature and information on the use of Paulliniae semen preparations [ESCOP 2009; Haskell *et al.* 2007; Andersen 2001; Bérubé-Parent *et al.* 2005; Martinet *et al.* 1999; de Oliveira Campos *et al.* 2011; Da Costa Miranda *et al.* 2009].

In the studies on the "behavioural effects" of Paulliniae semen, the alertness and contentedness ratings were found significantly increased and dose-dependent. Also the "stimulant effects" for guarana seeds as well as the "improvement of fatigue and depression in cancer chemotherapy" were also tested, evaluating the effectiveness of *Paullinia cupana* seed extract on fatigue, sleep quality, anxiety, depression symptoms, and guarana seed significantly improved positive trends on mood.

Based on these published data, guarana seed powder appeared as a nontoxic herbal preparation for the short-term symptomatic treatment of fatigue, and its use is plausible in the proposed indication "Traditional herbal medicinal product for symptoms of fatigue and sensation of weakness".

## 5. Clinical Safety/Pharmacovigilance

### 5.1. Overview of toxicological/safety data from clinical trials in humans

#### 5.2. Patient exposure

A daily dose of 1 g of guarana seed powder containing 21 mg of caffeine and 160 mg of tannins, taken orally by 15 volunteers for 150 days, provoked tachycardia in 4 patients and “burning in the stomach” in other 3 patients [ESCOP 2009].

#### 5.3. Adverse events and serious adverse events and deaths

Diffuse severe muscle pain and myoglobinuria were observed in a 29-year old patient taking a combination preparation of 500 mg of guarana seed extract, 200 mg of *Ginkgo biloba* extract and 100 mg of kava-kava extract. No renal complications were observed. Muscle pain and blood creatine kinase abnormality gradually subsided within 6 weeks [ESCOP 2009].

A 25-year old woman with pre-existing mitral valve prolapse died after ventricular fibrillation following the ingestion of about 55 ml of a ginseng and guarana seed drink found to contain approximately 550 mg of caffeine. The post-mortem content of caffeine in aortic blood was found to be 19 mg/l; sclerosis and myxoid change of the mitral valve leaflets were observed [Cannon *et al.* 2001].

Anxiety, irritability and severe heart palpitations were observed in a 51-year old female smoker (without cardiovascular disease) after daily intake for over a month of 2-4 tablets of each of two herbal supplements, one containing 1000 mg of guarana seed and 80 mg of gotu kola per tablet, the other containing 200 mg of guarana seed and 100 mg of gotu kola per tablet. Complete recovery was observed within 10 days of discontinuing the supplements [ESCOP 2009].

One case of a 30 years old female patient presenting with a 48 hours-standing anuria, who permanently used products of grist of a virtuous plant, guarana and occasionally used a parenteral non-steroid painkiller. The clinical history and laboratory results showed acute renal and hepatic failure. The histological picture of the renal biopsy specimen verified an acute tubular necrosis. After temporary dialysis treatment, her renal function recovered progressively with compensatory polyuria [Vágási *et al.* 2007].

#### 5.4. Laboratory findings

No data available.

#### 5.5. Safety in special populations and situations

##### Special patient population

No data on the use in children and adolescents are available, therefore guarana seeds can only be intended for adults and elderly. The Community herbal monograph states that the use in children and adolescents under 18 years of age is not recommended, with a cross-reference to section 4.4 ‘Special warnings and precautions for use’ pointing to the lack of adequate data.

##### Fertility, pregnancy and lactation

Caffeine crosses the placenta and is distributed in breast milk.

In the absence of sufficient data and in accordance with general medical practice, it is recommended not to use the herbal medicinal products containing guarana seeds during pregnancy and lactation.

No fertility data available.

### **Overdose**

No cases of overdose have been recovered in the scientific literature.

### **Drug abuse**

No information in the literature search.

### **Effects on ability to drive or operate machinery or impairment of mental ability**

No data in the literature search.

### **Potential for interactions**

The potentiation of the action of psychoanaleptic drugs and caffeine-containing beverages is mentioned in the literature [Blumenthal 2000].

The potential for guarana seeds and their extracts to interact pharmacologically with a number of drugs, including -but not limited to- ephedrine, phenelzine, monoamine oxidase (MAO) inhibitors, adenosine, clozapine, benzodiazepines, propranolol and metoprolol, phenylpropanolamine and quinolone antibiotics, has been noted [Burdock *et al.* 2009].

## **5.6. Overall conclusions on clinical safety**

Based on empirical and experimental (partly on caffeine) evidence, at the recommended therapeutic dose, the use of guarana seed is safe. However, due to the lack of data confirming the safety, the use during pregnancy and lactation, and in children and adolescents is not recommended.

As there are no adequate data on genotoxicity, carcinogenicity and reproductive and developmental toxicity of guarana seeds, it is not possible, because of safety concerns, to establish a Community list entry.

## **6. Overall conclusions**

The positive effects of guarana seed extracts for symptoms of fatigue and sensation of weakness have been recognised since centuries empirically, while this use is plausible also by the existing *in vitro* and *in vivo* pharmacological data. There are also controlled clinical studies with preparations containing guarana supporting this indication, in particular the clinical studies in published literature reported above and information on the use of Paulliniae semen preparations [ESCOP 2009; Haskell *et al.* 2007; Andersen 2001; Bérubé-Parent *et al.* 2005; Martinet *et al.* 1999; de Oliveira Campos *et al.* 2011; Da Costa Miranda *et al.* 2009].

In conclusion, guarana seed powder can be used in traditional herbal medicinal products in the following indication:

‘Traditional herbal medicinal product for symptoms of fatigue and sensation of weakness’.

In the absence of adequate data in other populations, guarana seed is intended only for adults and elderly.

In the absence of sufficient data and in accordance with general medical practice, it is recommended not to use herbal medicinal products containing *Paullinia cupana* during pregnancy and lactation.

Moreover no serious adverse effects have been reported, this supports a safe use in the proposed traditional indication.

As there are no adequate data on genotoxicity, carcinogenicity and reproductive and developmental toxicity of Paulliniae semen, it is not possible, because of safety concerns, to establish a Community list entry.

## **Annex**

### ***List of references***