EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Camellia sinensis* (L.) Kuntze, non fermentatum folium

Based on Article 16(d)1, Article 16f and Article 16h of Directive 2001/83/3C as amended (traditional use)

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Camellia sinensis* (L.) Kuntze, non fermentatum folium
Herbal preparation(s)	• Comminuted herbal substance • Powdered herbal substance
Pharmaceutical form(s)	Herbal substance or comminuted herbal substance as herbal tea for oral use Herbal preparations in solid dosage forms for oral use.
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1. Introduction

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

- Herbal substance(s)

Green tea leaf (*Camelliae sinensis non fermentatum*, folium) consists of whole or cut young, unfermented, rapidly hot dried leaf of *Camellia sinensis* (L.) Kuntze and its cultivated varieties. It contains not less than 2.0% of caffeine ($C_8H_{10}N_4O_2$, Mr 194,2) (dried drug) (French Pharmacopoeia, 2010).

The fresh leaves of *Camellia sinensis* (L.) Kuntze (Fam. Theaceae), also known as *Thea sinensis* L., are processed in a manner designated to prevent the enzymatic oxidation of catechins. The enzymes are inactivated by heat (steam or pan-fried).

- Herbal preparation(s)

included in monograph:

- Comminuted herbal substance for herbal teas
- Powdered herbal substance

not included in monograph:

- Dry extract, purified (DER 45-56:1, extraction solvent: water) corresponding to 55-72% (-) epigallocatechin-3-O-gallate
- Dry extract, decaffeinated (DER 6:1 to 10:1, solvents such as alcohol, methanol, acetone, or water or mixtures of these solvents). It contains not less than 60.0 percent of polyphenols, calculated as (-)-epigallocatechin-3-O-gallate, not less than 40.0 percent of (-)-epigallocatechin-3-O-gallate, and not more than 0.1 percent of caffeine, calculated on the anhydrous basis.(USP34-NF29S2, Dietary Supplements)

Constituents (%, dried drug)

Gruenwald *et al.,* 2004; Balentine *et al.,* 1997; Ferrara *et al.,* 2001; Peterson *et al.,* 2005; Sharma *et al.*, 2007; Chacko *et al.,* 2010 Wang and Ho, 2009; Tsao, 2010:

Methylxanthines: caffeine (2.5 to 4.2%), theophylline (0.02-0.04%), theobromine (0.15-0.2%)

Flavonoids:

Flavonols: quercetin, kaempferol, myricetin mainly as 3-*O*-glycosides

Flavones: apigenin, luteolin as *C*-glucuronides

Flavanols: (flavan-3-ols 10-25%): (-)-epicatechin (EC), (-)-epicatechin-3-*O*-gallate (ECG), (-)-epigallocatechin (EGC) and (-)-epigallocatechin-3-*O*-gallate (EGCG)

Phenolic acids: including among others, chlorogenic acid, gallic acid, theogallin

Amino acids: 19 amino acids, amongst which theanine [5-N-ethyl glutamine (3% w/w)]

Terpene saponins (theafolia saponins): aglycones including among others, barringtogenol C, R1-barringenol

Polysaccharides (13 %)

Proanthocyanidins (tannins)

The effect of climatic conditions on green tea composition was investigated: variations of theanine and other amino acids (isoleucine, leucine, valine, alanine, threonine, glutamine), quinic acid, EC, EGC, EGCG and caffeine level are reported (Lee *et al.,* 2010).

- 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.

This assessment refers only to *Camelliae sinensis non fermentatum folium.*

1.2 Information about products on the market in the Member States

Spain (TU)

Preparations: powdered herbal substance
Preparations on the market: Registered product, 1986
Pharmaceutical form: capsules, hard, 250 mg
Therapeutic indication: adjuvant treatment of weight control diets
Posology: 2 capsules 3 times daily
Preparations: powdered herbal substance
Preparations on the market: registered product, 2006
Pharmaceutical form: tablets, 465 mg
Therapeutic indication: adjuvant treatment of weight control diets
Posology: 2 tablets twice a day

France (TU)

Preparations: powdered herbal substance
Preparations on the market: authorised product, 1986
Pharmaceutical form: capsules, hard, 390 mg
Therapeutic indication: traditionally used in functional asthenia; traditionally used as an adjuvant of slimming diets
Posology: 1 capsule 3 times daily (up to 5 capsules daily if necessary)

Germany (marketing authorisation)

Preparations: purified dry extract from Camelliae sinensis non fermentata folia (45-56:1) corresponding to 55-72% epigallocatechin gallate (extraction solvent: water)
Preparations on the market: authorised product, 31.08.2009
Pharmaceutical form: ointment
Therapeutic indication and posology: cutaneous treatment of external genital and perianal warts (*condylomata acuminata*) in immunocompetent patients from the age of 18 years, up to 0.5 cm string of ointment (=250 mg) 3 times daily (1 g ointment contains 100 mg purified dry extract)
Preparations: purified dry extract from *Camelliae sinensis* non fermentata folia (45-56:1) corresponding to 55-72% epigallocatechin gallate
Preparations on the market: authorised product, 07.09.2011
Pharmaceutical form: ointment
Therapeutic indication and posology: cutaneous treatment of external genital and perianal warts (*condylomata acuminata*) in immunocompetent patients from the age of 18 years, up to 0.5 cm string of ointment (250 mg) 3 times daily (1 g ointment contains 100 mg purified dry extract)

Risks (adverse drug effects, literature):

The following undesirable effects have been observed and reported during treatment with purified dry extract from Camelliae sinensis non fermentata folia, with the following frequencies:

General disorders and administration site conditions:
Very common (≥1/10): Local reactions at the application site like erythema, pruritus, irritation/burning, pain, ulcer, oedema, induration and vesicles
Common (≥1/100 to <1/10)*:* Local reactions at the application site like exfoliation, discharge, bleeding and swelling;
Uncommon (≥1/1,000 to ≤100)*:* Local reactions at the application site like discolouration, discomfort, dryness, erosion, fissure, hyperaesthesia, anaesthesia, scar, nodule, dermatitis, hypersensitivity, local necrosis, papules, and eczema

Blood and lymphatic system disorders:
Common (≥1/100 to <1/10): lymphadenitis, lymphadenopathy

Infections and Infestations:
Uncommon (≥1/1,000 to ≤100): application site infection, application site pustules, herpes simplex, infection, pyoderma, staphylococcal infection, urethritis, vaginal candidiasis, vulvovaginitis and vulvitis

Renal and urinary disorders:
Uncommon (≥1/1,000 to ≤100): dysuria, micturition urgency, pollakisuria and urethral meatus stenosis

Reproductive system and breast disorders:
Common (≥1/100 to <1/10): phimosis
Uncommon (≥1/1,000 to ≤100): balanitis, dyspareunia, and vaginal discharge

Skin and subcutaneous tissue disorders:
Uncommon (≥1/1,000 to ≤100): Rash and papular rash

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Details not known
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products registered
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products registered
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products registered
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products registered
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products registered
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products registered
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products registered
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products registered
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products registered
Romania	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products registered
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products registered
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products registered
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known

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.

Despite green tea is widely used, just a few herbal preparations has been marketed so far in EU.

1.2. Search and assessment methodology

Databases: Scopus, Medline, PubMed

Search terms: Green tea, Camellia sinensis folium

Libraries: Carol Davila University of Medicine and Pharmacy, Faculty of Pharmacy, Bucharest

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

According to Gardner *et al.,* 2007, tea is the most consumed beverage in the world after water. Green tea is most commonly used in Asia, especially in Japan and China. It was introduced in Europe as beverage by the Dutch East India Company around 1610. The tea initially imported into Europe was green tea. Green Tea (*Thea viridis*,) (*Camelia viridis*) was included in Culpeper's Complete Herbal (1880) as diuretic, stomachic and useful in headache. The stimulant action on nervous system is mentioned as a side effect.

In 'Precis de Matiere Medicale', tea (*Thea sinensis* Sims *sin. Camellia Thea* Link.) is introduced as the only important, from the medical point of view, representative of the Camelliaceae. Details on preparation and sources of tea are included. As therapeutical indications, the external use as solution with astringent properties and the internal use (infusion, 4 – 10 g per 100 ml water) as tonic and digestive, mild diuretic in arthritis, diaphoretic and general stimulant (with no distinction between green and black tea) are listed (Leurier *et al*, 1946).

Used first during the Song Dynasty (960-1279) the fine powder of green tea leaves, called 'tea mud' is no longer popular in China but it is still widely used in Japan. The cultivation of tea in Japan was initiated in the 11th century by Zen Buddhist monks who also developed methods for processing and preparing the powdered green tea known as 'matcha'. In Japanese "cha" means tea, and "ma" means powder. According to the serving method the entire leaf in powder form is ingested as suspension in hot water. One serving size is usually prepared by using 2-3 g of matcha powder. (http://www.domatcha.com/matcha, http://www.obubutea.com/tea-info/how-to-make-matcha-tea)

In Handbuch der Pharmacognosie a short history of green tea in Japan and the description of traditional method of preparation are also included (Tschirch, 1923).

Taking into account the historical use of *Camellia sinensis* and the information about products on the market in the Member States the requirements of at least 30 years in medicinal use and at least 15 years of use in the Community as requested by Directive 2004/24/EC for qualification as traditional herbal medicinal product are fulfilled for the herbal substance and herbal preparations specified in the monograph (comminuted and powdered herbal substance) in the proposed indications.

No proposals can be made for the two dry extracts listed as herbal preparations.

No information on products in Europe containing a decaffeinated dry extract described in USP34-NF29S2, Dietary Supplements have been found.

The purified dry extract, DER 45-56:1 (extraction solvent: water) corresponding to 55-72% EGCG is on the market in Europe since August 2009 as an ointment with marketing authorisation based on a full dossier.

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

According to Culpeper, "Green Tea (Thea viridis, Camellia viridis) is diuretic, and carries an agreeable roughness with it into the stomach, which gently astringes the fibres of that organ, and gives such a tone as is necessary for a good digestion: the Bohea is softening and nutritious, and proper in all inward decays. Strong tea is prejudicial to weak nerves, but is salutary for violent headache and sickness occasioned by inebriation (Culpeper, 1880).

According to Gruenwald *et al.* (2004) green tea is used internally for stomach disorders, migraine, symptoms of fatigue, vomiting and diarrhea when taken as a beverage (unproven use). It can be used to increase performance (stimulant effect). Due to caffeine content, the drug has a centrally stimulating, antidepressant and diuretic effect. The inotropic positive effect, stimulating effect on gastric acid secretion, glycolysis and lipolysis are also reported (Gruenwald *et al.,* 2004).

Chinese medicine uses green tea to treat migraine, nausea, diarrhoea resulting from malaria and digestion problems. It is also used as a cancer preventive (Gruenwald *et al.,* 2004).
Leung(1980) in Duke (1983) reports the use of tea for neuralgic headaches.

In India, tea preparations are traditionally used for diarrhea, loss of appetite, hyperdipsia, migraine, cardiac pain, fever and fatigue (Gruenwald *et al.,* 2004).

Duke and Wain (1981) in Duke, J.A. (1983) report that the traditional use as analgesic, antidote, astringent, cardiotonic, carminative, CNS-stimulant, demulcent, deobstruent, digestive, diuretic, expectorant, lactagogue, narcotic, nervine, refrigerant, stimulant, and stomachic; used for bruises, burns, cancer, cold, dog bite, dropsy, dysentery, epilepsy, eruptions, fever, headache, hemoptysis, hemorrhage, malaria, ophthalmia, smallpox, sores, toxemia, tumors, and wounds. There are no differentiations among the commercial categories of tea.

In Potter's Herbal Cyclopaedia the following medicinal uses of tea are reported: stimulant and diuretic due to caffeine content, astringent due to polyphenols with shown results in diarrhoea. The effectiveness of green tea extract treatment in weight loss is cited. (Williamson, 2003)

Khare C.P. (2007) indicates the stimulant, diuretic and astringent action of tea. Hypocholesterolaemic and hypoglycaemic activity of green tea are also included. Leaves are good appetizer, stomachic, diaphoretic, diuretic, detergent and resolvent; as well as useful in thirst, hemicrania, pain in the heart, piles, and inflammations. Young leaves and the alkaloid caffeine contained in it are astringent, stimulant and diuretic. Caffeine is extensively used in modern practice and is of great value in migraine, hemicrania, neuralgia and other nervous affections. Tannins contained in the leaves are astringent. Tea catechols improve capillaries and small blood vessels function. It is also used against poliomyelitis, rheumatism and infection of respiratory organs and radiation diseases. (Bokhtear, 2011)

Uses as food:
As a stimulant drink in form of infusions, of ready-to-drink beverages on the basis of dried green tea extract or beverages prepared by the consumer from instant green tea powder, or as non stimulant beverage (decaffeinated green tea).

As food supplements in solid form, or as a drink in many cases on the basis of dried green tea extracts. (EFSA, 2009)

Information from literature:
Whole or comminuted herbal substance for herbal preparation, 1.8-2.2 g tea/bag.

Preparation: boiling water is poured over a heaped teaspoon of leaf tea, a level teaspoon of crushed leaves or a tea bag and left to steep for 3-10 min. The caffeine is almost completely drawn after approximately 3 min. The tannin-containing substance increases when the tea is left to brew.

Daily dosage: a daily dose of 300-400 mg polyphenols is typical. The amount of polyphenols in 3 cups of green tea is between 240-320 mg. (Gruenwald *et al.,* 2004)

The indication proposed by MLWP-HMPC:
Traditional herbal medicinal product for relief of fatigue and sensation of weakness.

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

A 180 ml serving (6 ounces) of tea contains approximately 60 mg of caffeine, compared with approximately 100 mg of caffeine in a 180 ml serving of freshly brewed coffee. Black, green, and oolong tea beverages contain about the same amount of caffeine when prepared using the same amount of leaves. The amount of caffeine in tea beverage is determined by the brewing conditions of time, temperature, leaf size, and amount of tea. (Balentine *et al.*, 1997)

Doses corresponding to 300 mg caffeine (5 cups of tea as a beverage) are reported as the maximum accepted daily intake. (Gruenwald *et al.,* 2004*)*

According to Gruenwald a daily dose of 300-400 mg of polyphenols is typical. One cup of Green Tea normally contains 50-100 milligrams polyphenols. The amount of polyphenols in 3 cups of Green Tea is between 240 and 320 mg. (Gruenwald *et al.,* 2004)

Health Canada, in a 2010 information update, recommends that healthy adults do not exceed 400 mg of caffeine per day. According to the same source, a serving size of green tea (237 ml) contains approximately 30 mg of caffeine. (http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2010/2010_40-eng.php, March 2012.)

Posology based on information received from the Member States (France, Spain): Adjuvant treatment of weight control diets and functional asthenia: 1,170 to 1,950 mg of powdered herbal substance daily (corresponding to approximately 35 - 80 mg of caffeine).

Posology based on information received from the Member States (France) and Gruenwald *et al*. (2004):

Adults and elderly:

Herbal tea: 1.8-2.2 g of whole or comminuted herbal substance in 100 – 150 ml of boiling water as a herbal infusion, 3-5 times daily

Herbal substance, powdered: 390 mg 3 to 5 times daily

The use in children and adolescents under 18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use')

Duration of use:

No information available.

Taking into account the indication, the proposed duration of use is 1 week.

If the symptoms persist longer than 1 week during the use of the herbal 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

Primary pharmacodynamics

Stimulant effects

Oral administration of 0.6% green tea (6 mg tea solids/ml) or 0.04% caffeine (0.4 mg/ml; equivalent to the amount of caffeine in 0.6% green tea) as the sole source of drinking fluid to SKH-1 mice for 15 weeks increased 24 h locomotor activity by 47% and 24%, respectively (p <0.0001). Oral administration of 0.6% decaffeinated green tea (6 mg tea solids/ml) for 15 weeks increased locomotor activity by 9% (p <0.05). The small increase in locomotor activity observed in mice treated with decaffeinated green tea may have resulted from the small amounts of caffeine still remaining in the decaffeinated green tea solutions (0.047 mg/ml). (Michna, 2003)

Singal (2005, abstract only) investigated the protective effect of green tea extract (GTE)-no data regarding composition- and catechin in the mouse model of chronic fatigue syndrome (CFS). Animals were subjected to a forced swimming test session of 6 minutes every day for 7 days; a significant increase in immobility time on successive days represented the CFS in mice. Biochemical analysis revealed that the chronic swim test significantly increased lipid peroxidation levels and decreased glutathione levels in mouse whole-brain homogenate. Treatment with GTE (25 or 50 mg/kg, i.p.) and catechin (50 or 100 mg/kg, i.p.) for 7 days reversed the increase in immobility time. Protection was correlated with the lowered levels of lipid peroxidation and restoration of reduced glutathione levels in the brains of fatigued mice.

Assessor's comments:
Caffeine is a mild stimulant, and this is the main basis of the use of green tea. Some of the pharmacodynamic properties of green tea may be interpreted on the basis of its caffeine content. Caffeine itself is sometimes given concomitantly with other analgesics to produce stronger and quicker pain-killing actions, but there is no information of a similar application of green tea. Caffeine increases free fatty acids and glucose levels in plasma. The underlying mechanism of action for these effects is generally regarded to be a selective blockade of adenosine receptors via competitive inhibition, which are present in brain, blood vessels, kidneys, heart, gastrointestinal tract and respiratory passageways (Burdock, 2009).

The well-known stimulant effects of caffeine, the main xanthine constituent, were already extensively described in other Community monographs on herbal medicinal products containing caffeine (like Mate folium, Colae Semen and Paulliniae semen) and are aplicable also in this case to support the proposed indication.

The mild stimulant effect of green tea on the central nervous system, due to the amount in caffeine, was further demonstrated in vivo.

Secondary pharmacodynamics

Antioxidative effects

In vitro

The ability of tea catechins to act as a free radical scavenger, measured by standard reduction potential proved to be lower that of α-tocopherol (Table 1.)

Standard reduction potential for tea catechins, tea polyphenols and other physiological antioxidants- according to Balentine (1997).

Table1. Redox Potentials of Catechins, Gallocatechins, Quercetin,and Rutin.

Component	1st redox potential (V)
Epigallocatechin (EGC)	0.09
Quercetin (Q)	0.11
Gallocatechin (GC)	0.13
Epigallocatechin gallate (EGCG)	0.14
Gallocatechin gallate (GCG)	0.15
Epicatechin (EC)	0.19
Epicatechin gallate (ECG)	0.20
Catechin (C)	0.20
Rutin (R)	0.23
Gallic acid (GA)	0.25

Tea polyphenols may also inhibit the formation of reactive oxygen species by inhibiting the enzymes, like xanthine oxidase.

Aucamp *et al.* (1997) reported the inhibition of xanthine oxidase by five tea catechins. The K_i values (µM) were 303.95 for C, 20.48 for EC, 10.66 for EGC 2.86 for ECG and 0.76 for EGCG. The Ki of EGCG was almost similar to the one of allopurinol (0.30), exerciting the most potent effect.

Lin *et a*l. (2000) investigated in cultured human leukemia cells (HL-60 cells) the inhibitory effects of tea polyphenols EGCG from green tea and theaflavin from black tea, namely theaflavin (TF1), theaflavin-3-gallate (TF2), theaflavin-3,3'-digallate (TF3), gallic acid and propyl gallate (PG) on xanthine oxidase activity. Theaflavins and EGCG inhibit xanthine oxidase,TF3 acting as a competitive inhibitor and is the most potent inhibitor among these compounds. EGCG and theaflavins have potent inhibitory effects (>50%) on phorbol myristate acetate (PMA) -stimulated superoxide production at 20 approximately 50 µM in HL-60 cells. Gallic acid showed no inhibition under the same conditions. At 10 µM, only EGCG, TF3, and PG showed significant inhibition with potency of PG > EGCG > TF3.

Gallic acid, EGC and EGCG can inhibit lipopolysaccharide- induced iNOS gene expression and iNOS activity in cultured macrophages. iNOS activity in lipopolysaccharide- activated macrophages treated with EGCG (5 and 10 mM) for 6–24 hours was significantly lower than that in macrophages without EGCG treatment. Electrophoretic mobility shift assay indicated that EGCG blocked the activation of nuclear factor-kB, a transcription factor necessary for iNOS induction (Lin *et al*., 1997)

Long *et al.* (2000) indicated that addition of 1 mM of EGC, EGCG or quercetin to commonly used cell culture media leads to generation of substantial amounts of hydrogen peroxide .

In vivo

Administration of tea and catechins has been reported to prevent or attenuate decreases in antioxidant enzyme activities in a number of animal models of oxidative stress.

In hypercholesterolemic rabbits, green tea extract (GTE) and black tea extract administration in their drinking water (3 g/l) increased plasma α- tocopherol concentrations after 8 and 17 weeks of tea

administration, but not after 21 weeks. GTE contained 28.5% (w/w) catechins including EGCG (10%) and EGC (7%), ECG (5%) and EC (4%), while black tea extract contained approximately 6% catechins, 1.2% theaflavins, 2% flavonols and thearubigens. The total plasma antioxidant capacity was not affected by green or black tea administration over the 21-weeks study period (Tijburg *et al*., 1997).

Yuan *et al.,* 2006 examined the effect of EGCG on alcohol-induced gut leakiness, and explored the related mechanisms involved in its protection against alcohol-induced liver injury in rats. EGCG supplementation (at dose of 100 mg/kg) partly blocked the gut leakiness, reduced endotoxemia and lipid peroxidation, and blunted the elevated expressions of CD14, TNF-α, COX-2 and iNOS, which were associated with improved liver injury.

Augustyniak *et al.*, 2005 (only abstract available) investigated the influence of green tea on the liver antioxidant potential of different aged rats chronically intoxicated with ethanol. The ethanol diet caused a significant decrease in activity of antioxidant enzymes (SOD, catalase), while administration of green tea (7 g/l) to ethanol-treated rats for 5 weeks partly normalized the activity of SOD and catalase. Green tea caused a decrease in lipid and protein oxidation in ethanol-treated rats. The protective effect of green tea was confirmed by the significantly lower activity of biomarkers of liver damage [alanine aminotransferase (ALT) and aspartate aminotransferases (AST)] in the serum of rats that received green tea with ethanol compared with rats from the control ethanol group.

Agarwal *et al.*, 1993 (only abstract available) observed that oral feeding of 0.2% GTE (w/v) for 30 days to SKH-1 hairless mice followed by irradiation with UVB (900 mJ/cm^2) resulted in significant protection against UVB radiation-caused cutaneous oedema ($p<0.0005$) and significantly inhibited UVB-induced decreases in epidermal catalase and glutathione reductase activities ($p<0.01$).

Effects on glucose tolerance and insulin sensitivity

Wu *et al*., 2004 examined whether GTE has an effect on glucose tolerance and insulin sensitivity in Sprague-Dawley rats. The GTE used contained: 18.53 mg/g EC, 21.51 mg/g ECG, 57.87 mg/g EGC and 199.49 mg/g EGCG. 0.5 g extract was dissolved in 100 ml water. After 12 weeks of green tea supplementation, the green tea group had lower fasting plasma levels of glucose, insulin, triglyceride, and free fatty acid than the control rats. Insulin-stimulated glucose uptake of adipocytes and insulin binding to adipocytes were significantly increased in the green tea group. Same authors observed *in vitro* that green tea polyphenols (0.075%) significantly increased basal and insulin-stimulated glucose uptake of adipocytes.

In addition, Potenza,*et al.,* 2007 observed that spontaneously hypertensive rats, which are often used as a genetic model of the metabolic syndrome, fed a diet supplemented with 200 mg EGCG/ kg/day for 3 weeks, insulin sensitivity was increased.

Wolfram *et al*., 2005 (only abstract available) investigated the antidiabetic effects of a highly purified extract containing 94% EGCG, 5% and 3% ECG in rodent models of type 2 diabetes mellitus and H4IIE rat hepatoma cells. Dietary supplementation with 0.25%, 0.5%, and 1% EGCG for 2 weeks resulted in reductions of glucose levels in food-deprived mice by 23.0%, 35.2%, and 47.6%, respectively. The effects was dose-dependent. Plasma concentrations of triacylglycerol were reduced and glucose-stimulated insulin secretion was enhanced. In H4IIE cells, EGCG down-regulated genes involved in gluconeogenesis and the synthesis of fatty acids, triacylgycerol, and cholesterol. EGCG decreased the mRNA expression of phosphoenolpyruvate carboxykinase in H4IIE cells as well as in liver and adipose tissue of db/db mice. Glucokinase mRNA expression was upregulated in the liver of db/db mice in a dose-dependent manner.

Metabolic effects including effect on body weight

Richard,*et al.,* 2009 investigated if regular decaffeinated green tea intake (as drinking fluid), for 6 weeks could modulate body weight in an experimental model of obesity (male leptin-deficient (*ob*/*ob*) mice and their C57BL/6J lean littermates). Green tea leaves contained 1.38 mg/g EC, 4.45 mg/g GC, 32.21 mg/g EGC, 21.04 mg/g EGCG, 5.51 mg/g EG. The tea was prepared as 2 g leaves/100 ml in 0.5% citric acid buffer. Administration of decaffeinated green tea to *ob*/*ob* mice significantly slowed their rate of weight gain, as compared with control group (fed with buffer alone). This effect is apparent after only 1 week of supplementation ($p<0.05$). No significant difference was recorded between C57BL/6J lean mice administrated decaffeinated green tea and the control group. Decaffeinated green tea consumption by *ob*/*ob* mice was also associated with significantly lower cholesterolemia, triglyceridemia, and adiponectin concentration. Fecal lipids did not change significantly throughout the experiment.

Kim *et al.*, 2009 (only abstract available) further examined the efficacy of GTE in the B6.V-Lep ob/J (ob/ob) leptin-deficient mice. Mice were fed a high-fat diet supplemented with 0.5 mg/g dietary GTE (containing 55% EGCG, 15% EGC, 21% ECG, and 8% EC; w/w) for 12 weeks. GTE treatment induced a significant reduction in perirenal and total white adipose tissue weights compared with high-fat–fed control mice. Also, the treated mice had higher plasma HDL cholesterol (HDL-C) and lower hepatic triglycerides. There was no significant effect of GTE on body weight.

Bose *et al.,* 2008 studied the effects of EGCG, on high-fat–induced obesity, symptoms of the metabolic syndrome, and fatty liver in mice. In mice fed a high-fat diet (60% energy), supplementation with dietary EGCG treatment (3.2 g/kg diet) for 16 weeks reduced body weight gain, body fat percentage, and visceral fat weight (p <0.05) compared with mice without EGCG treatment. The body weight decrease was associated with increased fecal lipids in the high-fat–fed groups (p <0.05). EGCG treatment attenuated insulin resistance, plasma cholesterol, and monocyte chemoattractant protein concentrations in high-fat–fed mice (p <0.05). EGCG treatment also decreased liver weight, liver triglycerides, and plasma ALT concentrations in high-fat–fed mice (p <0.05). Histological examinations of liver samples revealed adecreased lipid accumulation in hepatocytes in mice treated with EGCG compared with high-fat diet-fed mice without EGCG treatment.

In another experiment conducted by the same authors (Bose *et al.,* 2008) on 3-month old high-fat–induced obese mice, short-term EGCG treatment (3.2 g/kg diet, 4 weeks) decreased mesenteric fat weight 36% and blood glucose 22% compared with high-fat–fed control mice (p <0.05). The decrease in body weight gain was not significant.

Wolfram,*et al.,* 2006 investigated the effect of GTE (90% EGCG), on high-fat/high-sucrose–fed C57bl/6J mice. Treatment with 10 mg/g dietary GTE resulted in decreased body weight gain, plasma glucose, plasma triglycerides, and plasma leptin compared with controls. In the same study, the authors reported that 4-weeks treatment with 10 mg/g dietary GTE could reduce body weight gain and body fat weight in obese Sprague-Dawley rats. Gene expression studies revealed that green tea treatment decreased adipose mRNA levels of fatty acid synthase and acetyl CoA carboxylase-1.

Ito, 2008 investigated the effect of tea extract (1 and 5 g/l in the drinking fluid) administered for 3 weeks in male Wistar rats fed a normal-fat diet (10% energy). The extract used contains 55.5% EGCG, 19% (EC, ECG, EGC) and 0.6% caffeine. The 0.5% extract-treated group had significantly decreased body weight compared with the water-treated control group. Both tea extract groups had lower levels of serum cholesterol, serum triglycerides, and bile acids compared with the control group; these values were dose dependent. Mesenteric and liver lipids were also dose dependently reduced compared with the water-treated group.

Yang *et al.*, 2001 compared the effects of ethanol-soluble fractions prepared from various types of tea (green tea, Oolong tea and black tea) administered in drinking fluid 1% (w/v) in rats fed a high-sucrose diet. Extraction was done with 95% ethanol (DER 1:10), at the composition of green tea extract was: EGC 13.51%, EC 3.97%, EGCG 20.16%, ECG 7.88%; for oolong extract the composition was EGC 17.83%, EC 3.19%, EGCG 19.06%, ECG 5.77%; black tea extract contained EGC 1.72%, EC 2.15%, EGCG 1.35%, ECG 0.67%. Both Oolong and black tea extract-treated rats, but not GTE treated rats, had decreased body weight gains (28.8–35.0%) and feeding efficiency (19.8–32.2%). Hypertriglyceridemia was normalized by green and black tea drink on day 18 and by oolong tea extract on day 25, respectively. Hypercholesterolemia was normalized by green tea on day 18 and by oolong tea and black tea on day 25, respectively. Plasma HDL-cholesterol concentrations were not affected by any tea extract. The triglyeride content in the liver as well as the cholesterol content in the heart of rats fed sucrose-rich diet were elevated and were normalized by all types of tea drink tested.

Kao *et al.*, 2000 showed that intraperitoneal injection of EGCG (>98% pure), but not other catechins-EC, EGC, and ECG—caused acute body weight loss in male and female Sprague-Dawley rats within 2–7 days of treatment. EGCG also significantly reduced or prevented an increase in body weight in lean and obese male and female Zucker rats. The effective dose of EGCG was initially 30–50 mg EGCG/kg body weight. However, rats gradually adapted within 1 week and higher doses of EGCG (100 mg/kg body weight) were needed to reduce or prevent increases in body weight. The loss in body weight was reversible; when EGCG administration was stopped, animals regained the lost body weight.

Lean and obese male Zucker rats injected intraperitoneally with 70–90 mg EGCG/kg/day lost 10–13% of their body weight relative to their initial weight and 25% of their body weight relative to the control after 8 days of treatment (Kao *et al.*, 2000), but the weight-loss effect of EGCG in rats may have been due to a reduction in food intake, because male lean and obese Zucker rats injected intraperitoneally with EGCG consumed almost 50–60% less food than did control rats.

Lu *et al.,* 2001 showed that oral administration of green tea, black tea (6 mg tea solids/ml), decaffeinated green tea plus caffeine, decaffeinated black tea plus caffeine, or caffeine alone to normal SKH-1 mice for 4 or 8 weeks decreased the weight of the parametrial fat pads and the thickness of the dermal fat layer, but the decaffeinated teas had little or no effect. None of the treatments had an effect on body weight or food consumption. Tea administration did not affect body weight also in adrenalectomized mice. Oral administration of EGCG (2 mg/ml- which is equivalent to the concentration of total catechins in 0.6% green tea) for 2 or 4 weeks had no effect on the weight of the parametrial fat pad nor the thickness of the dermal fat layer.

Murase *et al.*, 2006 investigated the effects of 15 weeks intake of GTE (that contain EGCG (41%), EGC (23%), ECG (12%), EC (9%), GC (7%), caffeine(0.1%) in combination with regular exercise on the development of obesity in C57BL/6 mice. The authors compared body weight, adipose tissue mass, plasma parameters and β-oxidation activity in mice fed a low-fat diet (5% triglycerides), a high-fat diet (30% triglycerides), a high-fat diet supplemented with 0.5% (w/w) GTE, a high-fat diet in addition to swimming exercise or a high-fat diet plus 0.5% GTE in addition to swimming exercise for 15 weeks. GTE intake in diet (0.5% w/w) in combination with swimming exercise suppressed high-fat diet-induced body weight gain by 18% and 22%, respectively, compared to exercise and GTE intake on their own. Visceral fat accumulation and the development of hyperinsulinemia and hyperleptinemia were also reduced in the high-fat swimming exercise group. Muscular β-oxidation activity in this group was 69% and 52% higher, respectively, than that in the high-fat diet and high-fat plus GTE groups.

Murase *et al.*, *2005* investigated the effects of catechin-rich dry GTE on running endurance and energy metabolism during exercise in BALB/c mice after 8–10 weeks. The composition of GTE measured as 81% total catechin (41% EGCG, 23% EGC, 12% EG). Mice were divided into four groups: nonexercise control, exercise-control, exercise + 0.2% GTE, and exercise + 0.5% GTE groups. Running times to

exhaustion in mice fed 0.5% GTE were 30% higher than in exercise-control mice and were accompanied by a lower respiratory exchange ratio, higher muscle β-oxidation activity, and lower malonyl-CoA content. In addition, muscle glycogen content was high in the GTE group compared with the exercise-control group. Plasma lactate concentrations in mice fed GTE were significantly lower after exercise, concomitant with an increase in free fatty acids concentrations.

Kao *et al., 2000* observed that EGCG (purity > 98%), at dose of 85 mg/kg body weigth, administered intraperitoneally significantly reduced food intake in Sprangue-Dawley rats, body weight and blood levels of testosterone, estradiol, leptin, insulin, insulin-like growth factor 1, LH, glucose, cholesterol, and triglyceride; as well as growth of the prostate, uterus, and ovary.

Assessor'scomments:
The data on weight loss is inconsistent,not all the studies suggested a positive correlationand seems to be an adaptative response, sometimes reversible, in some cases is related with reduction of food intake, or with the administration of high doses of extracts or isolated compounds (EGCG), which are not relevant for oral human intake. The rodents' diets contain very high concentrations of fat (40–60% energy) or sugar that may not represent realistic consumption patterns. A stronger evidence on other symptoms of the metabolic syndrome was observed.

Antimicrobial activity

A decaffeinated methanolic extract of *Camellia sinensis* leaves (composition not investigated) showed *in vitro* antimicrobial properties against 111 bacteria, comprising 2 genera of Gram positive and 7 genera of Gram negative bacteria. Most of the strains were inhibited by the extract at 10-50 µg/ml concentrations and few strains were sensitive even at lower concentrations (5 µg/ml). The bacteria could be arranged in the decreasing order of sensitivity towards the compound in the following manner: *Staphylococcus aureus, Vibrio cholerae, Escherichia coli, Shigella spp., Salmonella spp., Bacillus spp., Klebsiella spp.* and *Pseudomonas aeruginosa* (Bandyopadhyay *et al.,* 2005)

The antibacterial activity was also confirmed *in vivo* in mice by the same authors. When it was given to Swiss strain of white mice at different dosages (30 or 60 µg/mouse), it significantly protect ($p<0.001$) the animals challenged with *Salmonella typhimurium* (Bandyopadhyay *et al.,* 2005)

In mice infected with *Mycobacterium tuberculosis*, oral administration of GTE (that contains approximately 70% catechins constituted by ECGC (45.05%), ECG (23.60%), EC (1.11%) and EG (0.02%) at dose of 10 mg/100 g body weight for 7 days attenuated decreases in erythrocyte GSH concentrations caused by the infection, and decreases in erythrocyte SOD activity (Guleria *et al*., 2002).

Dental Caries Prevention

Anti-cariogenic activity is related with bactericidal effect against *Streptococcus mutans* and *S. sobrinus*.

Otake *et al.,* 1991 (only abstract available) found that compared to other catechins EGCG and ECG were more active, 167 mg/l of EGCG caused 91% inhibition of glucosyltransferase activity of *S. mutans* JC-2 (c).

Xu *et al.,* 2011 found that ECGC inhibited growth of S. mutans planktonic cells at an MIC of 31.25 µg/ml and a minimal bactericidal concentration of EGCG at sub-MIC levels inhibited acidogenicity and acidurity of *S. mutans* cells.

S. mutans adherence to saliva-coated hydroxyapatite was substantially inhibited by ECGC at doses higher than 2 mg/ml (Hirasawa *et al.,* 2006)

Significantly lower caries scores were observed in specific pathogen free rats infected with *S. mutans* JC-2 *(c)* and fed a cariogenic diet and/or drinking water containing 0.05% EGCG as compared with control rats *(*Otake *et al.,* 1991 only abstract available*)*

Anticancer

There are several reviews regading the protective effects of GTE and its catechins, especially EGCG against chemical carcinogens (Yang *et al.*, 2002, 2009; Ju *et al.,* 2007). According to Yang *et al.,* 2009, there are more than 133 published studies since 1991 on this topic (Table 2).

Table 2. Inhibitory effects of tea and tea constituents in animal models*

Site	Number of studies showing inhibitory effects	Numer of studies showing no inhibitory effects
Lung	20 (1)	2
Oral cavity	6	0
Oesophagus	4	0
Stomach	9	0
Small intestine	8	1
Colon	11 (3)	6
Skin	27 (1)	0
Prostate	4 (5)	0
Breast	10 (8)	0
Liver	7	1
Bladder	3 (1)	0
Pancreas	2 (2)	0
Thyroid	1	0

*The data were obtained by a literature search of PubMed from 1965 to 2008 of animal carcinogenesis models. The number of xenograft studies is shown in parentheses.

Inhibition of lung tumorigenesis by green tea, black tea and their constituents has been demonstrated in different animal models, including those induced by tobacco smoke related chemical carcinogens such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), benzo[a]pyrene, and N-nitrosodimethylamine as well as spontaneously developed lung tumors in A/J mice (Yang *et al.*, 2000; Ju *et al.,* 2007).

Inhibitory effects of tea against tumorigenesis in the digestive tract have been shown in 27 out of 33 studies (Ju *et al.,* 2007). The inhibitory effects of tea and tea polyphenols on intestinal tumorigenesis in mice have been consistently observed in different studies (Yin *et al.,* 1994; Orner *et al.*, 2003; Suganuma *et al.*, 2001; Ju *et al.*, 2005).

Ju *et al., 2005* showed that administration of EGCG at 0.02%–0.32% in drinking fluid dose-dependently inhibited small intestinal tumorigenesis in *Apc*$^{Min/+}$ mice, but caffeine did not have such an effect .Western blot analysis indicated that the EGCG administration resulted in increased levels of E-cadherin as well as decreased levels of β-catechin catenin in the nucleus, c-Myc, phospho-Akt, and phospho-Erk in the tumors.

Hao *et al., 2007* observed that in *Apc*$^{Min/+}$ mice, green tea standardized extract (0.12% in diet) decreased intestinal tumor multiplicity by 70.5%, but ECG (0.08% in drinking fluid) had no significant inhibitory effect.

There are also some studies on the effect of tea on prostate cancer, according to Ju *et al.*(2007). Gupta *et al.,* 2001 reported that oral infusion of the polyphenolic fraction isolated from green tea (0.1% as drinking fluid) significantly inhibited tumor incidence and burden in the prostate as well as

metastases to distant sites in an autochthonous transgenic adenocarcinoma of the mouse prostate (TRAMP). model.

Adhami *et al.,* 2004 found that this treatment decrease (IGF)-1, phosphor-Akt, and phosphor-Erk 1/2 levels, but increase IGF binding protein-3 (IGFBP-3) levels in the prostate cancer of TRAMP mice.

Cytotoxicity

The cytotoxicity of green tea components was tested in rat hepatocytes *in vitro* and turned out to be highest with EGCG and to decline in the following order: EGCG > propylgallate > ECG > EGC > EC (Galati *et al.*, 2006*).*

In vitro studies by Schmidt *et al.,* 2005 showed that high concentrations (100-500 µg/ml) of green tea extracts (containing 47.5-52.5% polyphenols) can damage rat hepatocytes. In a separate series of experiments EGCG (at concentration of 200 µM) was identified as the cytotoxic compound, in contrast with EC, caffeine and theanine. The authors concluded that extremely high concentrations were required *in vivo*, taking into account the low oral bioavailability of catechins.

In vivo- see Chapter 3.3. Toxicological data

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

Absoption

Chen *et al.* 1997 investigated the absorption of EGCG, EGC and EC in rats after administration of decaffeinated green tea dry aquoeus extract that contained 73, 68, and 27 mg/g of EGCG, EGC and EC, respectively. After intragastric administration of the extract (200 mg/kg), bioavailability of EGCG was low in rats (1.6%) in comparison to 31.2% for EC and 13.7% for EGC.

Swezey *et al*., 2003 (only abstract available) also investigated the absorption of radiolabelled EGCG (administered orally in single dose, 250 mg/kg) in beagle dogs. This study found that approximately 20% of EGCG is absorbed systemically in beagle dogs, which is higher compared with in rats.

Zhang *et al.,* 2004 showed that EC, EGC, ECG and EGCG have a limited transepithelial absorption across small intestine by Caco-2 monolayer model with relatively small permeability coefficient values, this also indicates a low bioavailability.

Kim *et al.,* 2000 investigated the kinetics of EC, EGC and EGCG following repeated oral administration of a GTE in male Sprague-Dawley rats for 28 days. The GTE contained 86, 76, and 590 mg/g EC, EGC, and EGCG (ratio approximately 1: 0.9: 6.9 (w/w/w)). The tea extract was dissolved in drinking water and was provided as 0.1% and 0.6% (w/v) solution ad libidum. Although EGCG was the major catechin in the dosing solution (about 7-times more EGCG than EC or EGC), considerably lower systemic total EGCG concentrations were achieved. The plasmatic levels of EC and EGC were comparable.

A comparison of total and free plasma catechin concentrations showed that EC and EGC were mostly available in their conjugated forms. Over the 28-day treatment cycle, only between 4.5% and 10.6% free EC and between 4.4% and 13.6% free EGC were detected when compared to the total EC and EGC plasma concentrations. In contrast, between 39.3-78.8% of the total EGCG levels were available as free or unconjugated EGCG during the 28-day treatment period.

Distribution

Zhu *et al.*, 2001 investigated the distribution of EC, ECG and EGCG in male Sprague-Dawley rats following intravenous administration of a decaffeinated extract of catechins from *Camellia sinensis*.

This extract contained 5% EC, 13% ECG, and 50% EGCG (ratio: 1: 2.6: 10 (w/w)). The extract was administered as single dose of 50, 100, 200 and 300 mg/kg. A two-compartment model was used to describe the disposition profile of the three catechins. Following intravenous administration, the three catechins demonstrated a rapid distribution with distribution half-lives ($t^{1/2}$) of 3-15 min. Across the doses studied, EC, ECG, and EGCG showed similar central volumes of distribution ranging from 0.2 to 0.7 l/kg. The steady state volumes of distribution of the three catechins were about 3- to 4- fold higher than their central volumes of distribution, this suggested that the three catechins exhibited a relatively high degree of tissue distribution. Elimination of EC, ECG and EGCG was slower when compared to distribution.

The maximum plasma levels of the three catechins differed, but corresponded relatively to their respective amount in the dosing formulation.

Kim *et al*., 2000 studied in female A/J mice the distribution of EC, EGC and EGCG. A polyphenol preparation containing 86, 76, and 590 mg/g EC, EGC, and EGCg (ratio approximately 1: 0.9: 6.9) was administered at 0.6% (w/v) in water ad libidum for a period of up to 12 days. The catechin levels were generally higher in the lung when compared to the liver. In the lung, EGCG levels were considerably higher than EGC and EC levels. EGC and EC concentrations in the lung exceeded those observed in plasma. In the liver, EGC levels were slightly higher than EGCG levels and higher than EC levels. EGC distributes more to the lung and liver than EGCG.

Suganuma *et al*., 1998 evaluated the distribution of ^{3}H-EGCG in male and female CD-1 mice after gastric intubation. The authors describe that EGCG is widely distributed into various organs and that the liver is one of the target organs of EGCG. A second administration of the substance after a 6 hours interval enhanced tissue levels of radioactivity in blood, brain, liver, pancreas, bladder and bone 4-6 times above those after a single administration.

Lambert *et al.*, 2003 also investigated the distribution of EGCG following a single intragastic (163,8 µmol/kg) and an intravenous dose (21.8 µmol/kg) of EGCG in male CF-1 mice. Following intravenous administration, the highest EGCG levels (unconjugated form) were found in small intestine, lung, and liver. Lowest levels were observed in the prostate and the spleen with about 10- and 3-fold lower levels, as were found in the lung or in the liver. EGCG concentrations in the small intestine and the colon were substantially higher following intragastric administration compared to intravenous administration. EGCG levels in the prostate, liver, and lung were lower after oral than after intravenous administration.

Chen *et al.*, 1997, investigated the distribution of EC, EGC and EGCG in rat tissue following intravenous administration of a GTE. This catechin extract contained 27, 68, and 73 mg/g EC, EGC and EGCG (ratio 1:2.5:2.7). After intravenous dose of 25 mg/kg the highest level of EGCG was observed in the intestine. The lung, kidney, and liver were between 4- and 16- fold less exposed to EGCG than the intestine. Exposure in the liver was about 9.4-fold lower than in plasma. EGC and EC were also found primarily in the kidney, lung, and intestine whereas the liver was again least exposed in comparison to the other organs. However, EC and EGC were predominantly in the kidney compared to EGCG.

Metabolism

In general, the metabolism of catechins follows the same pathway in mice, rats and humans. The difference between the species was only observed with regard to quantitative differences between individual metabolites.

The main biotransformation pathways of EGCG are O-methylation by catechol-*O* methyltransferase (COMT) as well as glucuronidation and sulfation by glucuronosyl- and sulfatyl-*transferases.*

Zhu *et al.*, 2001 and Lu *et al.*, 2003 showed that *in vitro* O-methylation of EGCG occurred at the 4'- and the 4''- hydroxyl group giving rise to 4'-O-methyl-EGCG and 4''-O-methyl-EGCG as well as to the di-methylated derivative 4',4''-di-O-methyl-EGCG.

Meng *et al.*, 2002 identified *in vivo* four mono- and di-methylated metabolites from EGCG as conjugates in urine of mice following oral uptake of a GTE (0.6% solution). Among these metabolites, 4',4''-di-O-methyl- EGCG was the most predominant in mouse urine and was also detected in plasma and tissues. In relation to EGCG, 4',4''-di-O-methyl-EGCG was found at comparable levels in the urine or at about 2- to 4-fold lower levels in plasma, liver, kidney, small intestine, and faeces.

Four different monomethylated EGCG derivatives were found by Kida *et al.*, 2000, in bile fluid of rats, in addition to 4',4''-di-O-methyl-EGCG following oral uptake of 100 mg EGCG per animal. 4'-O-methyl-EGCG was present at about 10-fold lower levels than EGCG, but was the predominant metabolite in bile fluid. The O-methylated EGCG metabolites found in bile fluid were mostly glucuronide and sulfate conjugates similar to the non-methylated parent catechin EGCG.

Kohri *et al.*, 2001 revealed that the metabolism of catechins by intestinal bacteria involves cleavage of the 3-O-galloyl moiety yielding EGC and gallic acid as well as cleavage of the heterocyclic ring of EGCG to a hydroxyphenyl-propan-2-ol derivative, followed by subsequent formation of differently hydroxylated phenyl-valerolactone derivatives.

Excretion

Suganuma, 1998 observed that the excretion of EGCG occurred in the mice predominantly *via* faeces. Only about 0.6% of the administered EGCG is excreted via the urine. In rats, 32% and 35% of the EGCG dose was excreted via the urine and faeces within 72 hours. (Kohri*,* 2001*)*

Kohri *et al.,* 2001 also showed that after intravenous administration of [4-^{3}H]EGCG to bile-duct cannulated rats, the radioactivity of the bile sample excreted within 48 h accounted for 77.0% of the dose, whereas only 2.0% of the dose was recovered in the urine. The excretion ratio of bile to urine was calculated to be about 97:3, clearly showing that EGCG undergoes entero-hepatic cycling. The metabolite (4^{I},4^{II}-di-*O*-methyl-EGCG) was present in the conjugated form and made up about 14.7% of the administered radioactivity.

Kim *et al.*, 2000 studied the excretion of EC, EGC and EGCG after oral administration of a green tea extract in male Sprague-Dawley rats. The extract containing 86, 76, and 590 mg/g of EC, EGC and EGCG (ratio approximately 1 : 0.9 : 6.9) was administered as 0.6% (w/v) drinking water ad libidum for a period of up to 28 days. EGC was the predominant catechin in urine over the entire observation period of 21 days. Excretion of EC was considerably lower, while EGCG was not detected in urine. In contrast to excretion via the urine, EGCG was the predominant catechin in faeces, while EC was found at levels 3- to 4- fold lower than EGC in faeces, although similar amounts of EGC and EC were contained in the dosing formulation, indicating that excretion of EGC seemed to be higher than that of EC.

Zhu *et al.,* 2001 investigated the excretion of EC, ECG and EGCG following intravenous adminsitration of a decaffeinated extract of catechins from *Camellia sinensis* in male Sprague-Dawley rats. The catechin extract used contained 5% EC, 13% ECG, and 50% EGCG (ratio: 1: 2.6: 10). The excretion via the faeces of all three catechins in their free un-conjugated form was low in rats, up to 5% of the dose. Recovery of EGCG (0.6% to 1.0% of dose) and ECG (0.5% to 2.0% of dose) from the faeces was lower when compared to EC (2.7% to 5.1% of administered dose). Urine excretion of the unmodified catechin only seemed to play a role for EC. Up to 31% of the administered EC dose was recovered from the urine. ECG and EGCG were excreted via the urine at considerably lower proportions 2% and 5%, respectively).

Enzyme inhibition/induction

Wang *et al.*, 1988 investigated *in vitro* the inhibition of rat liver microsomal cytochrome P450 activity by isolated catechins. Purified catechins inhibited hydroxylase, deethylase and NADPH-cytochrom c reductase activity. The ID_{50} for EC, EGC, ECG and EGCG for aryl hydrocarbon hydroxylase were 1.0, 0.45, 0.1 and 0.08 mM.The activity of 7-ethoxyresorufin O-deethylase, 7-ethoxycoumarin O-deethylase and NADPH-cytochrom c reductase were similarly inhibited. Epoxide hydrolase was less inhibited. At a concentration of 1.0 mM, EC, EGC and ECG had little or no effect, whereas EGCG and the tea extract showed 40% and 39% inhibition.

Huynh *et al.,* 2002 confirmed the above findings. EGCG inhibited CYP2B1 activity at 0.1 mM and 0.25 mM by 26% and 31.6%.

Goodin *et al.*, 2003 investigated the effect of catechins on the activity and the levels of CYP450 isoforms in the liver of Swiss-Webster mice treated intraperitoneally with doses of ECG and EGCG of 12.5 and 25 mg/kg/day for 7 days. Treatment with EGCG resulted in increased levels and activities of CYP3A and CYP2E1, whereas CYP1A level and activity were not changed. In contrast, treatment with ECG, reduced the level and activity of CYP1A, whereas CYP3A and CYP2E1 remained unchanged.

Embola *et al.*, 2001 observed increased levels of a glucuronidated metabolite of 2-amino-3-methylamidazol-quinoline in rat urine after oral administration of green tea beverage (2%) for 6 weeks, showing an induction of UDP-glucuronosyltransferase activity.

Lu *et al.*, 2003 investigated *in vitro* the inhibition of COMT by catechins and their metabolites. ECG, EGCG was about 60-fold stronger than by EC, EGC, indicating that in the structure, the D-ring is important for inhibition. Methylated and glucuronidated EGCG derivatives still inhibited COMT, however, with different activities, such as 4''-glucuronidation of EGCG in the D-ring that had the strongest effects on the inhibitory activity (a 10-fold reduction in inhibition compared to EGCG). Methylation or glucuronidation of EGC in the B-ring greatly decreased COMT inhibition, whereas glucuronidation in the A-ring had little effect.

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

There are available toxicological data on herbal preparations but also on isolated constituents. Caffeine toxicityespecially its reproductive and developmental toxicity, has been assessed extensively by Brent *et al*, 2011. The authors concluded that in rodents caffeine does not increase the risk of embryonic death even at high dosages (exceeding 30 mg/kg/day) that produce toxic effects in parental animals.

Single dose toxicity

Herbal preparations

The acute oral LD_{50} of ECGC in mice has been reported to be 1390 mg/kg and intraperitoneal LD_{50} is 195mg/kg (Hara, 2001). Polyphenons (extracts with a mixture of catechins) have even higher $LD_{50,}$ suggesting extremely low toxicity of these. (Table 3.)

Table 3. Acute Toxicity of Tea Catechins

Tea Catechins	LD_{50} (Confidence limits) mg/kg		
	p.o.	i.p.	i.v.
EGCg	1390 (1248–1647)	150 (134–168)	195 (179–213)
Polyphenon 100	2142 (1977–2320)	166 (153–182)	
Polyphenon 60	2856 (2509–3252)	186 (168–207)	
Polyphenon 30	4647 (4378–4933)	240 (221–262)	
Polyphenon G	5576 (5253–5918)	232 (208–258)	232 (208–258)

Animals: ICR strain mice ♂ 7 weeks of age
Method of calculation: Van der Waerden

Repeat dose toxicity

Herbal preparations

Chan *et al.*, 2010 evaluated the toxicity of GTE in male and female F344/NTac rats and B6C3F1 mice treated with 0, 62.5, 125, 250, 500, or 1,000 mg/kg extract in de-ionized water by gavage 5 days/week for 14 weeks. The extract composition included GC (0.52 %), EGC (2.26 %), catechin (0.51%), EC (2.83%), CG (0.45%), caffeine (4.99%), EGCG (48.4 %), and ECG (12.8 %). In the rats, no treatment-related mortality was noted. In the mice, treatment-related mortality occurred in male and female mice in the 1,000 mg/kg dose groups. The cause of early deaths was likely related to liver necrosis. Treatment-related histopathological changes were seen in both species in the liver, nose, mesenteric lymph nodes, and thymus. In addition, in mice, changes were seen in the Peyer's patches, spleen, and mandibular lymph nodes. The no adverse effect level (NOAEL) for the liver in both species was 500 mg/kg. In the nose of rats, the NOAEL in males was 62.5 mg/kg, and in females no NOAEL was found. No NOAEL was found in the nose of female or male mice.

Sakamoto *et al.*, 2001 investigated in a 13-week feeding study in F344/Du Cij rats the effects of an GTE containing 32.1% EGCG, 17.7% EGC, 8.5% EC, 3.3% GCG, 10.7% ECG, and 1.4% CG. The extract was administered in the diet in concentrations of 0, 0.625, 1.25, 2.5 and 5% of the polyphenol fraction, corresponding to EGCG doses of 0, 141, 283, 566 and 1132 mg EGCG/kg/day. The mean thyroid weight of the rats fed a diet containing 5.0% of the polyphenol fraction (5.0%-group) significantly increased to 444% of the control in males and to 304% of the control in females. Histological examinations of the thyroid of the 5.0%-group revealed marked hypertrophy and/or hyperplasia of the follicles. Slight hypertrophy of follicular cells was observed in male rats of the 1.25%-group and female rats of the 2.5%-group. Degree and incidence of thyroid lesions were higher in males than in females in the 1.25 %-, 2.5%- and 5.0%-groups. The induction of goitre by GTE catechins at high doses may be due to antithyroid effects of catechins. The NOAEL of the polyphenol fraction based on histological changes of the thyroid was considered to be 0.625% in males and 1.25% in females in the diet, corresponding to 141 and 283 mg EGCG/kg/day, respectively.

Johnson *et al.*, 2001 (only abstract available) mentioned a 13-week gavage study in Sprague-Dawley rats (20 animals/sex and group) which were treated with polyphenol fraction from green tea (53.4% EGCG, 11.4% EGC, 9.1% EC, 5.1% GCG and 4.9% ECG) administered in doses of 0, 90, 300 or 1000 mg polyphenol fraction (that corresponds to 0, 48, 160, 534 mg EGCG/kg/day). Early mortality was observed in both genders in the highest dose group. Body weight gain, feed consumption, relative and absolute weight of the spleen and thymus were reduced dose-related. Histopathological findings were pancreatic necrosis, hepatic degeneration/necrosis, thymic necrosis/atrophy. The authors derived a No Observed Effect Level (NOEL) ≥ 90 mg/kg/day polyphenol fraction (that corresponds to 48 mg EGCG/kg /day.

In the same abstract (Johnson, 2001) is mentioned also a 13-week-study in beagle dogs (4 animals/sex and group) treated orally with the same polyphenol fraction by capsules in doses of 0, 60, 200 or 600 mg/kg/day, corresponding to 0, 32, 107, or 320 mg EGCG/kg/day. A NOEL of ≥ 600 mg/kg/day (320 mg EGCG/kg/day) was determined by the authors.

Bun *et al.,* 2006 (only abstract available) examined the serological parameters of liver function (ALT, AST, alkaline phosphatase, glutamyl transferase, total bilirubin) in a 12-week study in female Wistar rats. GTE, which had been obtained with water or 80% ethanol as a solvent were administered by gavage in doses of 1400 mg/kg/day or 2000 mg/kg/ day, respectively. The authors did not observe any characteristic signs of hepatotoxicity. The only significant change in the animals treated with the ethanol extract was an increase in total bilirubin values and, in the case of those treated with the aqueous extract, a reduction in total bilirubin values.

Isolated constituents (EGCG)

Isbrucker *et al*., 2006 examined the effect of EGCG in a 13-week feeding study in Sprague-Dawley rats receiving 0, 50, 150 or 500 mg EGCG/kg/day. Changes in feed intake, body weight, clinical and haematological data observed in the treated rats, were judged not to be treatment related. The only statistically significant haematological effect in female rats in the highest dose group at the end of the recovery phase was the increase in total bilirubin. The reduced oral toxicity can be explained in conjunction with the low bioavailability. The authors concluded that the no-adverse effect level (NOAEL for EGCG in rats was 500 mg EGCG/kg body weight per day.

In a 13-week oral study “pre-fed” beagles were given capsules containing an EGCG (91.8% purity) in doses of 0, 50, 300 or 500 mg/kg/day (corresponding to 0, 46, 275 and 460 mg EGCG/kg/day). These doses were administered divided into two times per day. Vomiting was the most obvious dose-dependent effect which decreased in the course of the study. The haematological and clinical parameters were normal. There were no clinical-pathological effects and no effects on feed consumption or body weight. The only treatment-related histopathological effect described by the authors was the occurrence of pigmentation in the villous tips in the duodenum of treated dogs. The same brown pigment was found in the liver Kupffer cells of one female in the highest dose group and associated with EGCG phagocytosis. As there were no histopathological changes in the corresponding tissues, the finding was not deemed to be toxicologically relevant by the authors and a NOAEL of 500 mg/kg/day was derived from the study for the EGCG preparation, corresponding to 460 mg EGCG /kg/day. *(*Isbrucker *et al.,* 2006*)*

Groups of 4 male and 4 female fasting beagles, which had been given no food for at least 15 hours, were given EGCG (80% purity) at doses of 0, 50, 150 or 500 mg/kg/day (referred to the pure substance 0, 40, 120 or 400 mg EGCG/kg/day) in capsules for 13 weeks. EGCG was isolated from the initial hot water extract of *Camellia sinensis* leaves with ethyl acetate and subjected to chromatographic separation followed by spray drying. Dose-depending vomiting and diarrhoea were observed in the medium and highest dose groups. Three animals (1 male, 2 females) in the highest- and 2 females in the mediumdose group died or were killed because of a moribund condition. These animals showed considerably reduced body weight and were anorexic for three weeks prior to death. In the highestdose group the male manifested severe proximal tubular necrosis in the kidneys and one female showed haemolytic anaemia, liver necrosis, fairly severe gastric erosions and basophilic degeneration of the renal tubules. One of the females in the medium-dose group also manifested liver necrosis, gastric erosion and myocardial necrosis. In the two upper dose groups all animals manifested elevated total serum bilirubin values and more or less marked elevations of the AST and ALT values. None of the surviving animals manifested liver necrosis, but in the highest dose group one male was identified with proximal tubular necrosis of the kidneys and in one female renal tubular, degeneration

was observed. From the study the authors derived a NOAEL of 40 mg EGCG/kg/day (Isbrucker *et al.* 2006).

According to a published abstract by McCormick *et al*., 1999; Sprague-Dawley rats (20/sex and group) received oral doses of 0, 45, 150, or 500 mg EGCG/kg/day by gavage for 13 weeks. Toxicological endpoints included survival, body weight, food consumption, clinical signs, clinical pathology, ophthalmology, organ weights, gross pathology, and microscopic pathology. Early deaths in the high dose group and a dose-related suppression of body weight gain were seen in both sexes of rats. Microscopic findings suggesting possible alterations in gastrointestinal function included pancreatic necrosis and hepatic periacinar degeneration and necrosis; modest elevations in alkaline phosphatase, AST and ALT were seen in female rats in the high dose group. High dose rats of both sexes also demonstrated necrosis/atrophy of the thymus. According to the authors histopathologic data suggest that the NOEL of EGCG is 150 mg/kg/day in both male and female rats. However, body and organ weights appear to be more sensitive indicators of EGCG toxicity in male rats. On the basis of reduced body weight gain and decreased absolute and relative thymus weights, the investigators derive a NOEL for EGCG in male rats of 45 mg/kg/day. In a 13-week-study done by the same investigators, in which beagle dogs (4 animals/sex and group) were treated by oral doses of 0, 30, 100, or 300 mg EGCG/kg/day via capsules, a NOEL of ≥ 300 mg EGCG/kg/day was determined.

Genotoxicity

Herbal preparation

The mutagenic potential of a decaffeinated green tea dry extract (containing 51.4% EGCG and other catechins) was assessed in a range of established *in vitro* and *in vivo* test models such as Ames test, mouse lymphoma cell assay, micronucleus assay in mice and Big Blue transgenic mouse mutation assay. It was assessed in Ames test using *Salmonella typhimurium* (strains TA-98, TA-100, TA 1535, TA 1537) and E.coli strain WP2uvrA with and without metabolic activation; S9 mix prepared from rat liver was used as the activation system (4 and 10%). The standard method was used (plate-incorporation assay). Six concentrations of extract ranging from 156.2 to 5000 µg/plate were tested and negative and positive controls were also included. The assay was carried out in accordance to OECD guideline 471. The results obtained did not provide any evidence to suggest that the extract has mutagenic activity (Chang *et al.*, 2003).

Clastogenic activity of the same decaffeinated GTE was assessed in L5178Y $tk^{+/-}$ mouse lymphoma cell assay. Mutations in the *tk locus* were evaluated in cells exposed to green tea preparation, with and without S9 activation for 4 h. The study was conducted according to OECD 476 Guideline. Six concentrations of green tea preparation were tested and positive MMS (methyl methansufonate) and EMS (ethyl methansufonate) controls as well as sterile water as vehicle control were also included. In the absence of S9 activation, the results were equivocal (the statistically significant increases in mutation frequency was observed only in one experiment). With S9 activation, a statistically significant increase of mutation frequency was observed in both experiments starting from 205 µg/ml (Chang *et al.*, 2003).

The green tea decaffeinated extract is well characterized but the manufacturing process includes multiple steps of purification, therefore the extrapolation of data to the herbal tea is not recommended.

A micronucleus assay was carried out on Swiss-Webster mice (10 males and 10 females per group) to establish the potential to cause chromosomal aberrations. The assay was carried out using oral single doses of green tea decaffeinated extract of 375, 750 and 1000 mg/kg. Positive control (urethane 300 mg/kg) and vehicle control were also included. Two sampling time were considered (after 24 h and

48 h). Under the conditions employed, there was no significant increase in the frequency ofmicronucleated polychromatic erythrocytes (Chang *et al.*, 2003).

Gene mutations were assessed in B6C3F1 Big Blue *lacI* transgenic mouse. Animals were treated 28 days with GTE, administered by gavage at dose levels of 500, 1000 and 2000 mg/kg/day. A positive control (urethane 50 mg/kg/day) was also included. Thetissues selected were liver, lung and spleen. There was no significant increases in the frequency of *lacI* mutantions in all tissues tested.(Chang *et al.*, 2003).

Isolated constituents (EGCG)

The mutagenic potential of EGCG (88.1-95% purity) was assessed in a range of established *in vitro* and *in vivo* test models (Ames test, mouse lymphoma cell assay and *in vivo* micronucleus test). It was assessed in Ames test using Salmonella typhimurium strains TA-97, TA-98, TA-100, TA-102 and TA 1535 with and without metabolic activation; S9 mix prepared from rat liver was used as the activation system. Two methods were used: pour plate and preincubation method. The assay was carried out in accordance with OECD Guideline 471. Five concentrations of EGCG ranging from 50 to 5000 µg/plate were tested and positive and negative controls were also included. The results obtained did not provide any evidence to suggest that EGCG has mutagenic activity (Isbrucker *et al.,* 2006).

Clastogenic activity of EGCG (77% purity) was assessed in L5178Y $tk^{+/-}$ mouse lymphoma cell assay. Mutations in the *tk locus* were evaluated in cells exposed to EGCG, with and without S9 activation for 3h and 24 h. The study was conducted according to OECD 476 Guideline. Five concentrations of EGCG were tested and positive NQO and MMS controls as well as vehicle control were also included. In the absence of S9 activation, no increase of mutation frequency compared with control was noticed, at concentrations up to 100µg/ml EGCG. With S9 activation, a statistically significant increase of mutation frequency was observed starting from 125 µg/ml EGCG (equivalent to 210 µM). So, EGCG was clastogenic in the murine cells (Isbrucker *et al.*, 2006).

A micronucleus assay was carried out on NMRI mice (5 males and 5 females per group) to establish the potential of EGCG to cause chromosomal aberrations. The assay was carried out using oral single doses of EGCG (91.9% purity) of 500, 1000 or 2000 mg/kg. Positive control demethylbenzanthracene (DMBA) and vehicle control were also included. Under the conditions employed, there was no significant increase in the frequency of micronucleated polychromatic erythrocytes (Isbrucker *et al.*, 2006).

Administration in diet to CD-1 mice (6 males and 6 females per group) for 10 days, doses of 4200, 8400, or 12600 ppm of EGCG (80% purity) did not increased the frequency of micronucleated polychromatic erythrocytes.

Micronucleus assay was also conducted in Wistar rats (5 males and 5 females per group), treated intravenous with EGCG (92.6% purity) with doses of 15, 25 nd 50 mg/kg/day on two consecutive days. EGCG did not increased frequency of micronucleated polychromatic erythrocytes.

Carcinogenesis

In an oral gavage carcinogenicity study, a green tea preparation (catechins 85-95% (w/w) of the preparation which includes more than 55% of EGCG), was administered daily for 26 weeks to p53 transgenic mice at doses up to 500 mg/kg/day. The treatment was not associated with an increased incidence of either neoplastic or non-neoplastic lesions in the organs and tissues examined (*FDA, 2006*).

The effects of dietary administration of GTE (that contains 91.2% catechins [GC 1.4%, EGC 17.6%, EC 5.8%, EGCG 53.9% and ECG 12.5% (w/w)]) were examined using a multi-organ carcinogenesis

model. Groups of 15 F344 male rats were initially treated with a single i.p. administration of 100 mg/kg body weight N-diethylnitrosamine, 4 i.p. administrations of 20 mg/kg body weight N-methylnitrosourea, 4 s.c. doses of 40 mg/kg bw 1,2-dimethylhydrazine, together with 0.05% N-butyl-N-(4-hydroxybutyl)nitrosamine for 2 weeks and then 0.1% 2,2´-dihydroxy-di-n-propylnitrosamine for 2 weeks, both in the drinking water, for a total initiation period of 4 weeks. GTE in the diet, at doses of 1.0 or 0.1%, was administered from 1 day before and during carcinogen exposure, after carcinogen exposure or both during and after carcinogen exposure. Further groups of animals were treated with carcinogen, 1% green tea catechins or basal + diet alone as controls. The numbers of small intestinal tumors (adenomas and carcinomas) per rat were significantly reduced in the groups treated with 1% GTE during (0.13 ± 0.35) and after carcinogen exposure (0.31 ± 0.48) and in those receiving 1% and 0.1% GTE both during and after carcinogen exposure (0.14 ± 0.36, 0.46 ± 0.97 respectively) as compared with the carcinogen alone group (1.07 ± 1.21). On the other hand, numbers of glutathione S-transferase placental form positive liver foci per cm^2 were slightly but significantly increased in the groups treated with 1 and 0.1% GTE during carcinogen exposure, 1% GTE after carcinogen exposure and 1% GTE both during and after carcinogen exposure. According to the authors the results indicated that while GTE inhibits small intestinal carcinogenesis it slightly enhances hepatocarcinogenesis in a dose dependent manner when applied both during and after carcinogen exposure (Hirose *et al.*, 1993).

The International Agency of Research in Cancer (IARC) listed in 1991 green tea in group 3, meaning that is not classifiable as to its carcinogenicity to humans.

Reproduction and developmental toxicity *Herbal preparation*

An embryo-fetal development study was conducted in rats. Oral administration of a green tea preparation (catechins 85-95% (w/w) of the preparation which includes more than 55% of EGCG) during the period of organogenesis (gestational days 6 to 15) did not cause treatment related effects on embryo-fetal development at doses of up to 1,000 mg/kg/day (Faqi *et al.,* 2001).

Isolated constituents (EGCG)

EGCG (purity >91%) was administered to pregnant rats during organogenesis and development. Feeding pregnant rats diets supplemented at 1400, 4200 of 14,000 ppm during organogenesis was non-toxic to dams or foetuses. A two-generation study in rats fed 1200, 3600 or 12,000 ppm EGCG showed no adverse effects on reproduction or fertility. The highest dose reduced the growth rate of offspring, and there was a slight increase in pup loss. A growth effect among pups was also seen at 3600 ppm, but in the second generation only. The lowest dose was considered the overall NOAEL. The authors derived a NOAEL equivalent to 200 mg/kg body weight per day EGCG preparation. Because dams consumed twice the amount of feed during the crucial lactation period, in which effects occurred, twice the lowest dose which would normally have been 100 mg/kg body weight per day was calculated (Isbrucker *et al.,* 2006).

3.4 Overall conclusions on non-clinical data

Although a large variety of pharmacological effects have been reported for green tea and its constituents, for the proposed traditional oral use in functional asthenia, published data are limited. Nevertheless, it is sufficient to support the indication, taking into account the significant concentration of caffeine in herbal substance and the long-standing use. The caffeine content of green tea as herbal substance for herbal medicinal products is at least 2% (French Pharmacopoeia, 2010). The maximum daily dose proposed in the monograph (11 g of leaves) contains at least 220 mg caffeine. At this dose caffeine exhibits its stimulant effects (Burdock, 2009).

Regarding the use as adjuvant treatment in control of weight, the studies were conducted mainly on extracts or isolated compounds. The weight loss in animals is inconsistent and looks like an adaptative response, sometimes reversible. In some cases it is connected with reduction of food intake or with high doses administration of extracts or isolated compounds, which are not realistic for oral human use. The animal diets tested contained very high concentrations of fat (40–60% energy) or sugar that may not represent realistic consumption patterns. Also, the clinical data are inconclusive.

Other pharmacological studies provide only a theoretical background for the protective effects of green tea.

The bioavailability of green tea and its compounds in animals and humans is low, and the biotransformation is similar.

Several data regarding single-dose and repeat-dose toxicity, as well as on genotoxicity and reproductive toxicity and carcinogenicity have been reported.

With exception of mouse lymphoma cell assay, the other *in vitro* and *in vivo* studies on the mutagenic potential of decaffeinated GTE or EGCG have not shown any evidence of mutagenic activity.

Although that Ames test was negative, this was performed with a decaffeinated extract, taking into account that the manufacturing process to obtain the extract includes multiple steps of purification the extrapolation of these data to herbal tea is not recommended. These data can not support the inclusion to the Community list.

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

There are several human pharmacokinetic studies performed by different investigators.

Yang *et al.*, 1998 investigated in 18 volunteers the kinetics after oral administration of beverage containing decaffeinated GTE (1.5, 3.0, or 4.5 g) after overnight fasting. The plasma concentrations of EGCG, EGC, and EC reached peak levels between 1.5 and 2.5 h and declined to undetectable levels after 24 h. When the dose of green tea was increased from 1.5 to 3.0 g, the maximum plasma concentrations and the areas under the curve of EGCG, EGC, and EC increased 2.5- to 5-fold, but a further increase in dose to 4.5 g of green tea did not significantly alter these parameters. The half-lives of the terminal elimination phase of EGCG, EGC, and EC ranged from 3-5 h. The total amounts of EGC and EC excreted through the urine appeared to increase with increasing dose, but a dose-response relationship was not established. No EGCG was detected in the urine. Over 90% of the total EGC and EC was excreted between 0 to 8 h, and after 24 h, their levels were negligible. The bioavailability of EGCG appeared to be lower than EGC.

Catechins significantly differ in their pharmacokinetic profile. The catechins had been isolated from green tea by methanol, ethyl acetate and chloroform solvent extraction, and subsequently purified by column chromatography on Sephadex LH-20 with ethanol elution and double recrystallization from

water and final freeze drying and stored at -20^0 C. After oral administration of 1.5 mmole ECG, EGC or EGCG (99% purity), dissolved in 150 ml hot water to ten healthy volunteers in a randomized crossover design, catechin plasmatic levels were significantly diferent: EGC raises quickly with a short elimination half-life ($t^{1/2}$ elim = 1.7 h), ECG was intermediate in rise but slowest in decline ($t^{1/2}$ elim = 6.9 h), EGCG was slowest in rised but intermediate in decline ($t^{1/2}$ elim = 3.9 h). At 24 h, EGC and EGCG had returned to base levels, but EC was still elevated. Peak maximum varied between 1.3 EGCG and 5.0 EGC µmol/L EGC. Very limited interconversion fromECG to epicatechin or EGCG to EGC occurred, indicating that degallation is not required for uptake. Up to 13.6% of the ingested EGC (partly methylated) was excreted in the urine, while ECG or EGCG were not detected. *(*van Amelsvoort *et al.*, 2001*).*

After ingestion of 1.2 g of decaffeinated GTE (88 mg EGCG, 82 mg EGC and 33 mg ECG) in healthy volunteers, the plasmatic levels at 1 h were 46-268 ng/ml of EGCG, 82-206 ng/ml of EGC, and 48-80 ng/ml of EC, while ECG was not detected in plasma samples. The maximum urinary excretion of EGC and EC occurred at 3-6 h. Most of the EGC and EC were excreted in the first 9 h, and the cumulative urinary excretions in the first 24 h were 2.8-3.2 mg of EGC and 1.6-2.3 mg of EC. EGCG and ECG were not detected in the urine samples. (Lee *et al.*, 1995).

Natsume *et al.*, 2003 identified following three metabolites in human blood and urine after oral administration of EC: (-)-epicatechin-3'-*O*-glucuronide, 4'-*O* methyl-(-)-epicatechin-3'-*O*-glucuronide, and 4'-*O*-methyl-(-)-epicatechin-5 or 7-*O*-glucuronide.

Chow *et al.,* 2001 investigated the systemic bioavailability of green tea catechins after oral single-dose administration of EGCG capsules (200 mg EGCG/capsule) and green tea extract capsules (contain 200 mg EGCG, 37 mg EGC, 31 mg EC/capsule). Healthy subjects (five subjects/dose level) were assigned to receive one of the dose levels (200, 400, 600, and 800 mg based on EGCG content). All subjects were randomly crossed-over to receive the two catechin formulations at the same dose level. Comparing EGCG withGTE administration, plasmatic EGCG levels were similar (AUCs of unchanged EGCG were 22.5 vs. 21.9, 35.4 vs. 52.2, 101.9 vs. 79.7, and 167.1 vs. 161.4 mg/ml at the 200-,400-, 600-, and 800-mg dose levels, respectively). Comparing the relationship between AUC of EGCG and doses ingested, the authors concluded that the systemic availability of EGCG increases at higher doses, possibly due to saturable presystemic elimination mechanism. In plasma, EGCG was mainly present in the free form, whereas the plasma and urine EGC and EC were mostly in the form of glucuronide/sulfate conjugates.

Same authors also investigated the systemic availability of green tea catechins after 4 weeks of oral administration of EGCG capsules (200 mg EGCG/capsule) and GTE capsules (200 mg EGCG, 37 mg EGC, 31 mg EC/capsule). Eight healthy subjects were assigned per dose level to receive one of the five doses for 4 weeks (800 mg EGCG once/day, 400 mg EGCG twice/day, 800 mg EGCG and GTE once/day, 400 mg EGCG and GTE twice/day or placebo once/day). There was more than 60% increase in the AUC of EGCG after 4 weeks of administration at a dosing schedule of 800 mg one daily. No significant changes were observed in the kinetics of EGCG after repeated treatment at a regimen of 400 mg twice daily. EGCG was present mostly in free form (92%) in the systemic circulation. (Chow *et al.,* 2003)

Henning *et al.,* 2004 observed that plasmatic levels of EGCG were increased when is administered as extract, compared with consumption as green tea, even that the absorption is delayed in the first case.

Lee *et al.,* 2002 investigated the pharmacokinetic parameters of EGCG, EGC and EC after single oral dose administration of green tea or decaffeinated green tea (20 mg tea solids/kg) or EGCG (2 mg/kg) to eight subjects. The plasma concentration time curves of the EGCG, EGC, and EC were fitted in a one compartment model. The maximum plasma concentrations of EGCG, EGC, and EC in the three

repeated experiments with green tea were 77.9±22.2, 223.4±35.2, and 124.03±7.86 ng/ml, respectively. The time needed to reach the peak concentrations was in the range of 1.3–1.6 h. The elimination half-lives were 3.4±0.3, 1.7±0.4, and 2.0 ± 0.4 h, respectively. Considerable inter-individual differences and variations between repeated experiments in the pharmacokinetic parameters were noted. Significant differences in these pharmacokinetic parameters were not observed when EGCG was given in decaffeinated green tea or in pure form. In the plasma, EGCG was mostly present in the free form, whereas EGC and EC were mostly in the conjugated form. Over 90% of the total urinary EGC and EC, almost all in the conjugated forms, were excreted between 0 and 8 h. Substantial amounts of 4-*O*-methyl EGC, at levels higher than EGC, were detected in the urine and plasma. The plasma level of 4-*O*-methyl EGC peaked at 1.7±0.5 h with a halflife of 4.4±1.1 h. Two ring-fission metabolites,(-)-5-(3-,4-,5-trihydroxyphenyl)-valerolactone and (-)-5-(3-,4-dihydroxyphenyl valerolactone appeared in significant amounts after 3 h and peaked at 8–15 h in the urine as well as in the plasma.

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 is 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

Non controlled clinical study

After ingestion of a soft drink containing GTE enriched with L-theanine and theogallin (no other data on composition and dosage), EEG (electroencephalography) recorded 1, 2, 3 and 4 h after ingestion during different recording conditions revealed a general attenuation of electrical delta power under the condition of eyes open during the first hour ($p<0.01$). During a reading test increases of delta and theta power were observed at frontal electrode sites starting with the second hour after administration, significant at the third and fourth hour ($p<0.04$) in comparison to placebo. These changes indicate a higher level of mental performance. Visually evoked P300 potentials were recorded every hour in addition to the EEG recordings. Analysis of visually evoked P300 waves revealed a decrease in latency at the last hour ($p<0.04$) as well as increases of amplitudes at the electrode position Cz, suggesting an improvement of attention (Dimpfel *et al*., 2007).

Controlled clinical studies

The effect of a combination of GTE and L-theanine (LGNC-07) has been studied in a randomized, double-blind, placebo-controlled trial. The main outcome was the effect on memory and attention in subjects with mild cognitive impairment (MCI). Ninety-one MCI subjects whose Mini Mental State Examination-K (MMSE-K) scores were between 21 and 26 and who were in either stage 2 or 3 on the Global Deterioration Scale were enrolled in this study. The treatment group (13 men, 32 women; 57.58 ± 9.45 years) took 2 capsules with LGNC-07 (each capsule contained 360 mg GTE and 60 mg L-theanine), and the placebo group (12 men, 34 women; 56.28 ± 9.92 years) received an equivalent amount of maltodextrin and lactose for 16 weeks. Neuropsychological tests (Rey–Kim memory test and

Stroop color–word test) and electroencephalography were conducted to evaluate the effect of LGNC-07 on memory and attention. Further analyses were stratified by baseline severity to evaluate treatment response on the degree of impairment (MMSE-K 21–23 and 24–26). LGNC-07 led to improvements in memory by marginally increasing delayed recognition in the Rey–Kim memory test (p = 0.0572). Stratified analyses showed that LGNC-07 improved memory and selective attention by significantly increasing the Rey–Kim memory quotient and word reading in the subjects with MMSE-K scores of 21–23 (LGNC-07, n=11; placebo, n=9). Electroencephalograms were recorded in 24 randomly selected subjects hourly for 3 hours in eye-open, eye-closed, and reading states after a single dose of LGNC-07 (LGNC-07, n=12; placebo, n=12). Brain theta waves, an indicator of cognitive alertness, were increased significantly in the temporal, frontal, parietal, and occipital areas after 3 hours in the eye-open and reading states (Park *et al*., 2011).

In a randomised, double-blind, placebo-controlled study, healthy adult participants (n=48) received either 250 mg caffeine, 200 mg theanine, both or neither of these. Twohundred-and-fifty mg caffeine or 200 mg theanine corresponds to 6 cups of tea. They completed ratings of mood, including anxiety, and alertness, and had their blood pressure measured before and starting 40 min after drug administration. Anxiety was also assessed using a visual probe task. Caffeine increased self-rated alertness and jitteriness and blood pressure. Theanine antagonised the effect of caffeine on blood pressure but did not significantly affect jitteriness, alertness or other aspects of mood. Theanine also slowed overall reaction time on the visual probe task (Rogers *et al*., 2008).

Another study investigated the effect of a combination of 97 mg L-theanine and 40 mg caffeine as compared to placebo treatment on cognitive performance, alertness, blood pressure, and heart rate in a sample of young adults (n= 44). Cognitive performance, self-reported mood, blood pressure, and heart rate were measured before L-theanine and caffeine administration (at baseline) and 20 min and 70 min thereafter. The combination of moderate levels of L-theanine and caffeine significantly improved accuracy during task switching and self-reported alertness (both $p<0.01$) and reduced self-reported tiredness ($p<0.05$). There were no significant effects on other cognitive tasks, such as visual search, choice reaction times, or mental rotation (Giesbrecht *et al.*, 2010)

Assessor's comments:

The stimulatory activity of the green tea should be corroborated by its caffeine content. Concerning this, many studies confirm caffeine's ability to enhance mood and alertness (Kaplan et al., 1997; Lorist and Tops, 2003), awareness, attention, and reaction time (Cysneiros et al., 2007).

Weight loss

Non controlled clinical study

Ota *et al.*, 2005 showed positive results in young Japanese men consuming a green tea catechins beverage (570 mg catechins and 40 mg caffeine) as part of an exercise program (90 min/week) for 8 weeks. Fat oxidation was increased in the green tea catechins group under both exercising and sedentary conditions as compared to a placebo.

Hill *et al.,* 2007 failed to show differences in abdominal fat in overweight and obese Caucasian women consuming 300 mg/day EGCG (without caffeine) as part of a moderate-intensity exercise program (135 min/week) for 12 weeks compared to a placebo.

Dullo *et al.*, 1999 investigated the effect of GTE (containing 50 mg caffeine and 90 mg EGCG) in 24 -h energy expenditure (EE) and fat oxidation in humans. On 3 separate occasions, subjects (10 healthy men) were randomly assigned among 3 treatments: GTE (50 mg caffeine and 90 mg EGCG), caffeine (50 mg), and placebo. Relative to placebo, treatment with the GTE resulted in a significant increase in 24 h EE (4%; $p<0.01$) and a significant decrease in 24-h respiratory quotient (from 0.88 to 0.85;

p<0.001) without any change in urinary nitrogen. Treatment with caffeine in amounts equivalent to those found in the GTE had no effect on EE and respiratory quotient nor on urinary nitrogen.

Controlled clinical studies

Nagao *et al.*, 2005 investigated the effect of catechins on body fat reduction and the relation between oxidized LDL and body fat variables in healthy Japanese men. After a 2-week diet run-in period, subjects were divided into 2 groups with similar BMI and waist circumference distributions. A 12-week double-blind study was performed in which the subjects ingested 690 mg total catechins/day (EGCG, EC and EGC) (GTE group; n = 17) or 22 mg total catechins (control group; n =18). Body weight, BMI, waist circumference, body fat mass, and subcutaneous fat area were significantly lower in the GTE group than in the control group (*p* <0.01). Changes in the concentrations of malondialdehyde-modified LDL were positively associated with changes in body fat mass and total fat area in the GTE.

Positive findings were reported by Maki *et al.*, 2009 who compared the effects of a high-green tea extract-beverage (625 mg total catechins/day, including 214 mg EGCG, 207 mg EGC and 39 mg caffeine) versus a control beverage (39 mg caffeine) in 107 Caucasian subjects with increased central adiposity following a moderate-intensity exercise program (≥180 min/week) for 12 weeks. Reductions in abdominal fat area (−7.7 vs. −0.3%) and subcutaneous abdominal fat area (−6.2 vs. 0.8%), as measured by computerized tomography, were greater in the GTE group as compared to control, but only a marginal difference in body weight loss (−2.2 vs. −1.0 kg) was observed.

Belza *et al.*, 2007 investigated the effect of three different food ingredients: tyrosine, GTE and caffeine on resting metabolic rate and haemodynamics, on ad libitum energy intake (EI) and appetite in 20 healthy, normal weight men (age: 23.7±2.6 years). Subjects participated in a four-way crossover, randomized, placebo-controlled, double-blind study. Treatments were administered as tablets of 500 mg GTE, 400 mg tyrosine, 50 mg caffeine, or placebo, and were separated by more than 3-day washout. The acute thermogenic response was measured in a ventilated hood system for 4 h following ingestion. Blood pressure, heart rate, and subjective appetite sensations were assessed hourly and ad libitum EI 4 h post-dose. Caffeine induced a thermogenic response of 6% above baseline value (72± 25 kJ per 4 h) compared to placebo (*p* <0.0001). The thermogenic responses to GTE and tyrosine were not significantly different from placebo. Ad libitum EI was not significantly different between treatments but was reduced by 8%, 8% and 3% compared to placebo after intake of tyrosine, GTE and caffeine, respectively.

Venables *et al.*, 2008 reported that in healthy Caucasian men that ingested three capsules of GTE (890 mg total catechins and 366 mg EGCG/capsule) in the 24-h preceding a moderate-intensity exercise session a increase of fat oxidation by 17% compared to placebo was observed, suggesting that catechins amplify the effects of exercise on fat oxidation, possibly through increased lipolysis.

Auvichayapat *et al.,* 2008 (only abstract available) investigated in a randomized, controlled trial the effects of GTE (141 mg total catechins and 87 mg caffeine) on weight reduction in obese Thai population (60 obese subjects with BMI > 25 kg/m^2). All subjects consumed a Thai diet containing 3 meals (8373.6 kJ/day) for 12 weeks. Body weight, BMI, body composition, resting energy expenditure, and substrate oxidation were measured at baseline, and during weeks 4, 8, and 12 of the study. Serum levels of leptin and urine VMA (vanil mandelic acid) were measured at baseline and during the 12th week. Comparing the two groups, differences in weight loss were 2.70, 5.10, and 3.3 kg during the 4th, 8th, and 12th weeks of the study, respectively. At the 8th and 12th weeks of the study, body weight loss was significantly different (p<0.05). At the 8th week, the difference in resting energy expenditure was 183.38 kJ/day (p<0.001), the difference in the respiratory quotient was 0.02 (p<0.05), and no significant differences existed in satiety score, food intake, or physical activity. Urine VMA was significantly different in the 12 th week of the study (p<0.05).

In a double-blind, placebo-controlled clinical trial, the effect of GTE (491 mg catechins containing 302 mg EGCG) on 78 obese women (with BMI > 27 kg/m^2) and the relationship between GTE and obesity-related hormone peptides was investigated. The subjects were randomly divided into Groups A and B. Group A (n = 41) received GTE while Group B (n = 37) took cellulose as a placebo, one capsule (400 mg) three times each day for 12 weeks. The body weight, body mass index (BMI) and waist circumflex (WC) were measured at the beginning of the study and after 12 weeks of treatment with GTE. There was no statistical difference in % reduction in body weight, BMI and WC between the GTE and placebo groups after 12 weeks of treatment. Within group comparison revealed that the GTE group had significant reduction in LDL-cholesterol (LDL-C) and triglyceride, and marked increase in the level of HDL-C, adiponectin and ghrelin (Hsu *et al.,* 2008- only abstract available).

Hursel *et al.*, 2009 conducted a randomized, placebo-controlled, double-blind parallel trial in 80 overweight and moderately obese subjects [BMI: 29.6±2.0 in kg/ m^2] with a habitually low caffeine intake. A very-low-energy diet intervention during 4 weeks was followed by 3 months of weight maintenance (WM); during the WM period, the subjects received a green tea–caffeine mixture (270 mg EGCG and 150 mg caffeine/day) or placebo, both in addition to an adequate protein (AP) diet (50–60 g protein/ day) or an high protein (HP) diet (100–120 g protein/day). Subjects lost 7.0 ± 1.6 kg, or 8.2 ± 2.0%, body weight (<0.001). During the WM phase, WM, resting energy expenditure, and fat-free mass increased relatively in both the HP groups and in the AP and green tea–caffeine mixture group (p<0.05), whereas respiratory quotient and body fat mass decreased, all compared with the AP placebo group. Satiety increased only in both HP groups (p<0.05). The green tea–caffeine mixture was only effective with the AP diet.

The effect of a mixture of green tea and guarana extracts containing a fixed dose of caffeine and variable doses of EGCG on 24-hour energy expediture and fat oxidation was examined. Fourteen subjects were part in this randomized, placebo-controlled, double-blind cross-over study. Each subject was tested 5 times in a metabolic chamber to measure 24-hour energy expending 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 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 mixture compared with placebo. No effects of the ECGC- caffeine mixture was observed on lipid oxidation. Systolic diastolic blood pressure increased by about 7 and 5 mmHg, respectively, when the ECGC- caffeine mixture compared with placebo. The increase was significant only for 24-hour diastolic blood pressure. The increase in 24-hour energy expenture with ECGC- caffeine preparartion was similar with all doses of EGCG- in the mixture (Bérubé-Parent *et al.*, 2005- only abstract available)

Meta-analysis

Hursel *et al.,* 2009 meta-analysis includes 11 trials and the author's conclusion was that catechins or EGCG-caffeine mixture have a small positive effect on weight loss and weight maintenance. The effect on body weight loss was larger for Asian participants (−1.51 kg) versus Caucasian participants (−0.82 kg)

Cardiovascular disease

Coronary Heart Disease (CHD)

Nakachi *et al.,* 2000 assessed in a prospective cohort study the effect of green tea consumption on 8,552 Japanese citizens for a period of 12 years and reported a significant reduction in risk of death from CHD mortality among men (RR = 0.58; 95% CI[confidence interval]: 0.34–0.99) and a beneficial trend among women (RR = 0.82, 95% CI: 0.49–1.38) for those who consumed more than ten cups a day (1500 ml) of green tea, compared with those consumed 3 cups/day (450 ml).

Peters *et al.,* 2001 provided a meta-analysis of tea consumption (green and black) in relation to CHD as well as myocardial infarction and stroke based on ten cohort and seven case control studies. The study-specific effect estimates for stroke and coronary heart disease were too heterogeneous to be summarized (homogeneity p<0.02 for stroke, and p<0.001 for coronary heart disease). Only the relative risk estimates for myocardial infarction (seven studies) appeared reasonably homogeneous (homogeneity p = 0.20). The incidence rate of myocardial infarction is estimated to decrease by 11% with an increase in tea consumption of 3 cups/day (RR = 0.89, 95% CI: 0.79-1.01) (1 cup = 237 ml). However, the authors mentioned that the evidence of bias toward preferential publication of smaller studies make the results difficult to interpret.

Arts *et al.,* 2001 evaluated the association between catechin intake and the incidence of mortality from ischemic heart disease and stroke in the Zutphen Elderly Study, a prospective cohort study of 806 men aged 65–84 years. A total of 90 deaths from ischemic heart disease were documented. The mean catechin intake at baseline was 72 ± 47.8 mg, mainly from black tea, apples, and chocolate. Catechin intake was inversely associated with ischemic heart disease mortality (RR =0.49;95% CI: 0.27- 0.88; p =0.017). Catechin intake was not associated with the incidence of myocardial infarction (RR = 0.70; 95% CI: 0.39- 1.26; p = 0.232). After adjustment for tea consumption and flavonol intake, a 7.5-mg increase in catechin intake from sources other than tea was associated with a tendency of 20% reduction in ischemic heart disease mortality risk (p = 0.114). There was no association between catechin intake and stroke incidence or mortality.

Atherosclerosis

In the prospective Rotterdam Study conducted on 3,454 adults, 55 years of age or older and follow-up for 2-3 years, examination of aortic atherosclerosis via X-ray to measure calcified deposits in the abdominal aorta revealed that daily tea consumption is inversely associated with the development of severe aortic atherosclerosis. Odds ratios (ORs) decreased from 0.54 (95% confidence interval [CI],: 0.32-0.92) for drinking 125 to 250 ml (1-2 cups) of tea to 0.31 (CI: 0.16-0.59) for drinking more than 500 ml/d (4 cups/ day). The associations were stronger in women than in men. The association of tea intake with mild and moderate atherosclerosis was not statistically significant (Geleijnse *et al.,* 1999)

Sasazuki *et al.,* 2000 (only abstract available) investigated the relation between tea consumption and severity of coronary atherosclerosis in 512 Japanese patients (men and women) over 30 years of age and reported a protective effect of tea consumption in men, but not in women. In the men subgroup (n=262) significant stenosis ORs was 0.5 (95% CI: 0.2–1.2) for those consuming two to three cups of green tea and 0.4 (95% CI: 0.2–0.9) for those drinking four or more cups a day compared to subjects consuming one cup a day or less.

Hooper *et al.,* 2008 evaluated in a meta-analysis, that included 133 trials, the effectiveness of different flavonoid subclasses and flavonoid-rich food sources on cardiovascular disease and risk factors and observed that in 4 studies, green tea consumption (total catechins estimated daily intake 136 mg) reduced LDL (-0.23 mmol/l; CI :-0.34, -0.12) For many of the other flavonoids, there was insufficient evidence to draw conclusions about efficacy.

Stroke

Kuriyama *et al.,* 2006 (only abstract available) investigated the correlation between green tea consumption and mortality due to cardiovascular disease in Japan. The Ohsaki National Health Insurance Cohort Study, a population-based, prospective cohort study was initiated among 40,530 Japanese adults aged 40 to 79 years without history of stroke, coronary heart disease or cancer at baseline. Participants were followed up for up to 11 years (1995-2005) for all-cause mortality and for up to 7 years (1995-2001) for cause-specific mortality. Over 11 years of follow-up (rate, 86.1%), 4,209 participants died and over 7 years of follow-up (rate, 89.6%), 892 participants died of

cardiovascular disease and 1,134 participants died of cancer. Green tea consumption was inversely associated with mortality due to all causes and due to cardiovascular disease. The inverse association with all-cause mortality was stronger in women. In men, the hazard ratios of mortality due to all causes associated with different green tea consumption frequencies were 1.00 (reference) for less than 1 cup/day, 0.93 (95% CI: 0.83-1.05) for 1 to 2 cups/day, 0.95 (95% CI: 0.85-1.06) for 3 to 4 cups/day, and 0.88 (95% CI: 0.79-0.98) for 5 or more cups/day, respectively (p=0.03). The corresponding data for women were 1.00, 0.98 (95% CI: 0.84-1.15), 0.82 (95% CI: 0.70-0.95), and 0.77 (95% CI: 0.67-0.89), respectively (p<0.001). In women, the multivariate hazard ratios of cardiovascular disease mortality across increasing green tea consumption categories were 1.00, 0.84 (95% CI: 0.63-1.12), 0.69 (95% CI: 0.52-0.93), and 0.69 (95% CI: 0.53-0.90), respectively (p=0.004). Among the types of cardiovascular disease mortality, the strongest inverse association was observed for stroke mortality.

Liang *et al.,* 2009 studied the connection on tea consumption and ischemic stroke risk in a case–control study conducted in southern China from 2007 to 2008. A total of 374 patients with incident ischemic stroke and 464 control subjects (mean age: 69 years) were recruited. A significant decrease in ischemic stroke risk was observed for drinking at least one cup of tea weekly (p=0.015) when compared with infrequent or nondrinkers, the risk reduction being largest by drinking one to 2 cups of green or oolong tea daily. Significant inverse dose–response relationships were also found for years of drinking and the amount of dried tea leaves brewed. The adjusted ORs for the highest level of consumption in terms of frequency of intake, duration of drinking, and average tea leaves brewed were 0.61 (95% CI: 0.40 - 0.94), 0.40 (95% CI: 0.25 - 0.64), and 0.27 (95% CI: 0.16 -0.46), respectively.

Arab *et al.,* 2009 published a meta-analysis about green and black tea consumption and risk of stroke. Data from 9 studies involving 4,378 strokes among 194,965 individuals were pooled. The main outcome was the occurrence of fatal or nonfatal stroke. Regardless of their country of origin, individuals consuming 3 cups of tea per day had a 21% lower risk of stroke than those consuming 1 cup/ day (absolute risk reduction, 0.79 CI: 0.73 - 0.85).

Hypertension

In a prospective epidemiological study Yang *et al.*, 2004 studied the relation between tea drinking and risk of hypertension in 1,507 Taiwanese men and women aged >20 years with no history of hypertension. Six hundred subjects (39.8%) were habitual tea drinkers, defined by tea consumption of 120 ml per day or more for more than one year. Of these subjects 96.3% were green or oolong tea drinkers and 4.8% added milk to their tea. Compared with non-habitual tea drinkers, the risk of developing hypertension decreased by 46% for those who drank 120 to 599 ml/day and was further reduced by 65% for those who drank 600 ml/day or more after carefully adjusting for age, sex, socio-economic status, family history of hypertension, BMI, waist-hip ratio, lifestyle factors and dietary factors. However, tea consumption for more than 1 year was not associated with a further reduction of hypertension risk.

Diabetes

Iso *et al.,* 2006 describe a retrospective cohort study that included a total of 17,413 persons (6,727 men and 10,686 women, with age between 40 to 65 years old), all of them had no history of type 2 diabetes, cardiovascular disease, or cancer at the baseline lifestyle survey. During the 5-year follow-up, there were 444 self-reported new cases of diabetes in 231 men and 213 women (5-year event rates, 3.4% and 2.0%, respectively). Consumption of green tea and coffee was inversely associated with risk for diabetes 2. Multivariable odds ratios for diabetes among participants who frequently drank green tea and coffee (6 cups of green tea per day and 3 cups of coffee per day) were 0.67 (95% CI, 0.47 to 0.94) and 0.58 (95% CI, 0.37 to 0.90), respectively, compared with those who

drank less than 1 cup per week. Total caffeine intake from beverages was associated with a 33% reduced risk for diabetes. These inverse associations were more pronounced in women and in overweight men.

Hsu *et al*., 2011 examined the effect of a decaffeinated GTE on obese individuals with type 2 diabetes. The subjects were randomly assigned to either receive 1,500 mg of a decaffeinated GTE (providing a daily dose of 856 mg EGCG) or placebo daily for 16 weeks. Sixty-eight of 80 subjects, ages 20-65 years with BMI> 25 kg/m^2 and type 2 diabetes for more than one year, completed this study. Homeostasis model assessment for insulin resistance (HOMA-IR) was used as the major outcome measurement. At baseline and after 16 weeks of treatment, anthropometric measurements, fasting glucose, HbA1c, hormone peptides, and plasma lipoproteins were measured from both groups. No statistically significant differences were detected between the decaffeinated GTE and placebo groups in any measured variable. A statistically significant reduction in HbA1c (from 8.4 to 8.0%) was observed after GTE treatment compared to baseline. Within-group comparison also revealed that the GTE group had significant reductions in waist circumference, HOMA-IR index, and insulin level, and a significant increase in the level of ghrelin. Within-group comparison of those in the placebo group showed a significant increase in the level of ghrelin. This study found no statistical difference in any measured variable between the decaffeinated green tea and placebo groups.

Effect on cholesterol

Singh *et al.*, 2011 investigated the effects of green tea supplementation on the lipid profile of hypercholesterolemic subjects (23 males and 7 females of age between 35-60 years). Chemical analysis of green tea estimated the polyphenols, tannin and caffeine content at 10.2, 16.5 and 3.5 grespectively. The subjects taken were divided into two groups: experimental and control. The experimental group was supplemented with 3 cups (200 ml each) of green tea / day for 30 days. To estimate the effect of green tea on hypercholesterolemia subjects the anthropometric and lipid profile analysis was done before and after supplementation. No significant difference in height, weight and BMI was observed after supplementation. The significant reduction in total cholesterol and LDL levels in experimental group subjects was observed after supplementation. There was a reduction of 8.36% and 15.6%, respectively, in total cholesterol and LDL cholesterol levels of experimental group subjects.

In a randomised, placebo-controlled intervention trial, daily consumption of 2 cups of green tea/day (containing 250 mg total catechins),during six weeks did not affect serum total, LDL-, or HDL-cholesterol concentrations in 12 healthy women compared with 12 control women not consuming green tea. (Erba *et al.,* 2005)

In another parallel comparison trial, 45 volunteers (aged 18-65 years) were randomised to consume 900 ml per day (6 cups per day) mineral water, 3 g GTE (21.4% by weight catechins) or 3 g black tea extract (7.2% by weight catechins) diluted in the same amount of water (900 ml) for four weeks. Consumption of either green or black tea did not change significantly blood lipid concentrations as compared to controls. (van het Hof *et al.*, 1997)

Similarly in a placebo-controlled intervention trial with parallel design, healthy male and female smokers (aged 34$\pm$2 years, 13 to 16 subjects per group) consumed 6 cups (900 ml) of either black, green tea or water per day, or received as a supplement 3.6 grams of green tea polyphenols per day (2.5 g per day green tea catechins equivalent to the consumption of 18 cups of green tea per day) for 4 weeks. Consumption of black tea, green tea or green tea polyphenols had no effect on plasma triglycerides, total-C, HDL-C or LDL-C. (Princen *et al.,* 1998)

The effect of a theaflavin-enriched GTE, 375 mg per day (including 75 mg theaflavin, 150 mg green tea catechins, and 150 mg other green tea polyphenols), was studied in 120 Chinese subjects with mild to moderate hypercholesterolaemia in parallel comparison with another 120 subjects who

consumed placebo capsules. Main outcome measures were mean percentage changes in total-C, LDL-C, HDL-C, and triglyceride levels compared with baseline. After 12 weeks, the mean ± SEM changes from baseline in total-C, LDL-C, HDL-C, and triglyceride levels were -11.3% ± 0.9% (p =0.01), -16.4% ± 1.1% (p = 0.01), 2.3% ± 2.1% (p = 0.27), and 2.6% ± 3.5% (p = 0.47), respectively, in the tea extract group. The mean levels of total C, LDL-C, HDL-C, and triglycerides did not change significantly in the placebo group. No significant adverse events were observed. (Maron *et al.,* 2003)

Protection against oxidative damage

In a controlled human intervention study, a total of 143 heavy smokers (aged 18-79 years) were randomised to drink 4 cups per day of either decaffeinated green tea (73.5 mg/cup total catechins), decaffeinated black tea (8.11 mg/cup total catechins) or water during four months. Among the 133 smokers who completed the intervention, drinking green tea resulted in a significant decrease in urinary 8-OHdG (8-hydroydeoxyguanosine) assessed by ELISA (-31%) compared with water, while no significant change was observed among smokers consuming black tea. (Hakim *et al.,* 2003)

Cancer prevention

Several reviews were made regarding the protective effects of green tea consumption against cancer incidence (Boehm *et al.,* 2009; Tsubono *et al.,* 2001) but the results of epidemiological studies were inconclusive.

Fifty-one studies with more than 1.6 million participants were included in these reviews. Twenty-seven of them were case-control studies, 23 cohort studies and one randomised controlled trial. Twenty-seven studies tried to establish an association between green tea consumption and cancer of the digestive tract, mainly of the upper gastrointestinal tract, five with breast cancer, five with prostate cancer, three with lung cancer, two with ovarian cancer, two with urinary bladder cancer one with oral cancer, three further studies included patients with various cancer diagnoses.

Authors concluded that is insufficient and conflicting evidence to give any firm recommendations regarding green tea consumption for cancer prevention.

Dental Caries Prevention

A cross-sectional study of 6,014 14-year-old children in the UK found that, those who drank tea had significantly fewer dental caries than non-drinkers, regardless of weather they added sugar to their tea.(Jones *et al.,* 1999)

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

No data available.

4.3. Overall conclusions on clinical pharmacology and efficacy

The positive effects of preparations containing green tea against symptoms of fatigue and sensation of weakness are supported by the published data on green tea extracts (Dimpfel *et al.,* 2007; Parker, 2011)

The stimulatory activity of the green tea should be corroborated with its caffeine content. Taking into account that the minimum content in leaves is at least 2.0%, the maximum daily dose proposed in the monograph (11 g of leaves) contains at least 220 mg caffeine. At this dose caffeine exhibits its pharmacological effects in humans.

Other studies support different other effects (especially protective actions) but can not be connected with the traditional use of green tea.

The efficacy of green tea extracts on weight loss is small, inconsistent and no persistent effects were demonstrated. The meta-analysis results indicated a negligible effect.

5. Clinical Safety/Pharmacovigilance

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

Spain reported that in 2003, a product consisting of 375 mg of dry extract of *Camelia sinensis* (DER 4-8:1) extraction solvent: ethanol, 25% of catechins as EGCG, was withdrawn from the market due to hepatic adverse reactions.

There are some measurements taken by ANSM (French Health Products Safety Agency) on 7 April 2003 regarding the market authorization of a phytotherapeutical drug, recommended as adjuvant to weight-loss programs. This was suspended because the product was suspected of having caused hepatic disorders in 13 cases (9 in France, 4 in Spain), of which 4 cases were serious. One capsule contained 375 mg of a patented hydroalcoholic GTE, which was obtained using 80% ethanol as the extraction agent and which was standardised to 25% EGCG. Furthermore, the extract contained 5-10 % caffeine. The recommended dose was two capsules twice a day (daily dose corresponding to 375 mg EGCG). The withdrawn decision did not apply to other medicinal products composed of green tea (weak hydroalcoholic extract, aqueous extract and leaf powder) authorised in France (ANSM, 2003)

5.2. Patient exposure

Daily intake of green tea infusion or food supplements containing green tea components is reported by EFSA (European Food Safety Authority). According to EFSA the mean value for the consumption of green tea infusions is 362 g/person/day and the 95thpercentile is 1,097 g/person/day (EFSA, 2009). Referring to the catechin contents, the mean value corresponds to 95.2-147.7 mg/day EGCG and 186.4-307.3 total catechins.

Exposure with green tea components from food supplements may vary considerably (EFSA, 2009). Doses corresponding to 300 mg caffeine (5 cups of tea as a beverage) are reported in PDR 2004 as the maximum accepted daily intake.

The clinical trials reviewed by Nawrot *et al.,*2003 indicate that for the healthy adult population moderate caffeine intake (less than 400 mg caffeine per day, equivalent to 6.5 mg/kg bw/day for a 70-kg person) is not associated with any adverse effects such as general toxicity, cardiovascular effects, effects on bone status and calcium balance (with adequate calcium intake), changes in adult behaviour, increased incidence of cancer and effects on male fertility.

5.3. Adverse events and serious adverse events and deaths

Chow *et al.*, 2003 investigated the safety of green tea polyphenols after 4 weeks of daily oral. administration of EGCG, or a defined decaffeinated green tea polyphenol mixture (PTE). Healthy participants were randomly assigned to receive one of the five treatments for 4 weeks: 800 mg EGCG once/day, 400 mg EGCG twice/day, 800 mg EGCG as PTE once/day, 400 mg EGCG as PTE twice/day, or a placebo once/day (8 subjects/group). Adverse events reported during the 4-week treatment period include flatulence, upset stomach, nausea, heartburn, stomach ache, abdominal pain, dizziness, headache, and muscle pain. All of the reported events were rated as mild events.

Hepatotoxicity

Molinari *et al.*, 2006 reported a case of a previously healthy 44-year-old female who presented Grade-1 encephalopathy and severe hepatotoxicity. She had taken diet pills (containing GTE 720 mg/day) for the past 6 months. There was no other factor reported to cause the jaundice (eg. social, alcohol, drug, family or travel). The patient developed coagulopathy and required ventilatory and intensive care support. The patient underwent cadaveric liver transplant and the explanted liver showed multiple patterns of hepatic necrosis with some areas of relatively preserved liver parenchyma demonstrating centrovenular necrosis and bridging necrosis.

Some time later, Jimenez-Saenz and Martinez-Sanchez, 2007 reported that the patient was on progesterone therapy and this could also be considered as a potential causal agent for the jaundice.

Bonkovsky *et al.,* 2006 reported a 37-year-old female patient who took a dietary product containing green tea extract, 383 mg/day, for 4 months. The GTE was standardised at 25% catechins expressed as EGCG and containing 5–10% caffeine. She presented similarities to the prior case and had no other causes of hepatitis identified. After a month the patient had recovered with normalized liver function tests. However, one year after thwincident the patient re-challenged herself with the herbal preparation for 1 month and presented again hepatic failure.

Jimenez-Saenz and Martinez-Sanchez, 2006 describe the case of a 45-year-old male patient who developed acute hepatitis (ALT: 1613 U/l, AST: 1033 U/l, GT: 394 U/l, direct bilirubin: 102 µg/dl, total bilirubin: 119 µg/dl) after 4-month consumption of 6 cups a day of an unknown marketed green tea (no further information regarding ingredients or manufacturing). Two months after the withdrawal, the serum levels returned to normal. When the patient resumed his green tea consumption after 6 weeks, elevated serum concentrations were again observed for ALT, AST, -GT and total bilirubin one month later.

Another case report from a 26-year-old female patient who developed acute hepatocellular hepatitis with jaundice and asthenia (ALT: 3314 U/l, AST: 1813 U/l, direct bilirubin: 6.5 mg/dl) after 2 cups/ day consumption for 4 months, of a green tea beverage for “weight-loss” (75% green tea leaves, 25% mint leaves in the starting material). After the beverage withdrawal the symptoms disappeared, but reappeared after re-exposure. The authors point out that pulegon contained in mint leaves is also hepatotoxic, but the liver damage observed was relatedto the green tea portion in the starting material of the beverage (Martinez-Sierra *et al.,* 2006).

Assessor comments

Other cases from 2 Member States have been reported regarding the safety of GTE. Taking into account that, in some cases, cofounders were identified and these adverse reactions were not observed on clinical trials, it is questionable to extrapolate these data on all herbal preparations containing green tea as the subjects reported a consumption of high daily doses of green tea for mainly weight loss purposes. The standardised GTE (25% catechins, 5–10% caffeine) is not comparable to the included herbal preparations in the monograph.

Hematologic

Mycrocytic anemia in infants consuming an average of 250 ml of green tea/day have been reported, which may be due to impaired iron metabolism *(*Gruenwald *et al.*, 2004)

5.4. Laboratory findings

No data available

5.5. Safety in special populations and situations

Drug interactions

The potentiation of the action of psychoanaleptic drugs and caffeine-containing beverages is mentioned in Blumenthal, 2000.Green tea extracts, particulary at high doses may interact with antihypertensives drugs, antiplatelet drugs or warfarin (Stokley's, 2009).

Caffeine interactions

Drug interactions related withcaffeine intake: Monoamine oxidase (inhibitors, (furazolidone, procarbazine and selegiline) and concomitant intake of large amounts of caffeine may produce dangerous cardiac arrhythmias or severe hypertension because of the sympathomimetic side effects of caffeine; concurrent use with small amounts of caffeine may produce tachycardia and mild increase in blood pressure.(Thomson Micromedex, 2007)

The reabsorption of alkaline drugs can be delayed because of chemical binding with the tannins in tea (Gruenwald *et al.*, 2004)

Green tea extract containing EGCG 4.52%, ECG 1.39%, EGC 2.57 added in meat at concentration of 0.1 mM reduced the nonheme-iron absorption (Samman *et al.*, 2001)

Special patient population

No data on the use in children and adolescents are available, therefore green tea leaves 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.No data on use in children and adolescents are available.

Fertility, pregnancy and lactation

The safe use of green tea for pregnant women is addressed in relation to its main constituents (i.e. caffeine and polyphenols).

Caffeine crosses the placenta and is distributed in breast milk.

In Martindale, 2011 it is concluded that due to the limitations in reviewed studies a firm conclusion on the association between caffeine intake and miscarriage can not be drawn. Data on other adverse effects such as preterm birth and congenital malformations were found inconclusive.

UK Food Standards Agency, NHS Heathcare professionals but also the American college of Obstetricians and Gynecologists have recommended that pregnant women should limit their caffeine intake to less than 200 mg of caffeine per day. At this level, caffeine does not appear to be a major contributing factor in miscarriage or preterm birth (ACOG, 2010)

Caffeine is approved by the American Academy of Paediatrics for use by breastfeeding mothers, but is restricted to less than 300 mg/day whilst breastfeeding (Liston, 1998)

Navarro-Peran *et al.,* 2005 demonstrated only *in vitro* on mouse lymphoma cell line (L1210) that isolated compounds (EGCG) inhibit the dihydrofolate reductase activity and suggested that this mechanism of action may explain the folic acid deficiency that was linked to high levels of maternal green tea consumption during the periconceptional period, this deficiency may induce high incidence of neural tube defects.

Assessor's comments:

Even that the folic acid deficiency is well known to be associated with high incidence of neural tube defects (including spina bifida) the correlation between neural tube defects and tea consumption is unproved. This correlation was investigated only for high consumption of tea, and only in a few epidemiological studies (Navarro-Peran et al., 2005, study referred to another article published by Correa et al., 2000). Moreover the quality of data is questionable (small number of participants), and did not took into account DHFR polimorfism (e.g. DHFR 19bp del/del genotype).

Other studies (Shiraishi et al., 2010) demonstrated that consumption of high amounts of green tea or oolong tea is associated with low circulating folate levels.
Developmental studies in rats did not reveal any fetal malformations after administration of a GTE or isolated compound.

In the absence of strong evidence requiring specific warnings and sufficient safety data, it is recommended, in accordance with general medical practice, not to use the herbal medicinal products containing green tea or at least to avoid large quantities of green tea during pregnancy and lactation (Gruenwald et al., 2004)

Overdose

Overdosage (quantities corresponding to more than 300 mg caffeine or 5 cups of tea as a beverage) can lead to restlessness, termor, and elevated reflex excitability. The first signs of poisoning are vomiting and abdominal spasm (Gruenwald *et al.*, 2004)

Drug abuse

No information on green tea preparations in the literature search was found

Due to a possible caffeine tolerance development also addressed in literature (Martindale, 2011) and in other Community monograph on herbal products containing caffeine, the duration of use is limited toone week.

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

No data in the literature search.

5.4. Overall conclusions on clinical safety

The potentiation of the action of psychoanaleptic drugs and caffeine-containing beverages is mentioned (Blumenthal, 2000). Green tea extracts, particulary at high doses may interact with antihypertensives drugs, antiplatelet drugs or warfarin (Stokley, 2009).

Taking into account the daily intake of green tea infusion as beverage reported by EFSA and the traditional use over a long period, green tea is considered to be safe, when it is used in the specified conditions.

Green tea dried extracts were involved in some cases of hepatotoxicity and gave reason for safety concerns. Hepatotoxicity is related with high doses of herbal preparations (elevated percentages of caffeine 5-10% and up to 25% on catechins) and with the cytotoxicity of EGCG exhibited at these levels. Taking into account that in some cases cofounders were identified and these adverse reactions were not observed on clinical trials, it is questionable to extrapolate these data on all herbal preparations containing green tea.

Considering the low bioavailability of EGCG and the real concentrations in green tea leaves, the actual risk for the use of green tea seems to be low.

Due to the lack of data confirming safety, the use in pregnancy, lactation, children and adolescents is not recommended.

6. Overall conclusions

Green tea has been used in traditional medicine for centuries in Asia and at least for 100 years in Europe. The herbal substance is described in French Pharmacopoeia.

The positive effects of green tea for symptoms of fatigue have been recognized since centuries empirically while this use is plausible also by the existing *in vitro* and *in vivo* pharmacological data.

Sufficient data are available to develop a Community monograph on the traditional use of *Camellia sinensis* (L.) Kuntze, non fermentatum folium. The indications are suitable for self-medication. The proposed indication is:

Traditional herbal medicinal product for relief of fatigue and sensation of weakness.

Taking into account its traditional use over a long period of time and the assessed scientific data, green tea is considered to be safe, when use in the specified conditions.

Green tea dried extracts were involved in some cases of hepatotoxicity and gave reason for safety concerns. Hepatotoxicity is related with high doses of such preparations consumed for different reasons than the proposed indication in the monograph (mainly for weight loss) and with the cytotoxicity of EGCG exhibited at these levels. Taking into account that in some cases cofounders were identified and these adverse reactions were not observed in clinical trials, it is questionable to extrapolate these data on all herbal preparations containing green tea. Considering the low bioavailability of EGCG and the real concentrations in green tea leaves, actual risk for the use of green tea in proposed daily doses seems to be low.

In the absence of sufficient data, the medicinal use of green tea is intended only for adults and should not be taken in children and adolescents under 18 years of age.

The use of the traditional herbal medicinal products is not recommended during pregnancy and lactation in the absence of available data.

The minimum required data on mutagenicity (Ames test) are available for herbal preparations of green tea leaves. Unfortunately these data can not be extrapolated to herbal substance, taking into account that the GTE used for such tests is purified.

As there are no adequate data on genotoxicity, carcinogenicity and reproductive toxicity of green tea leaves, it is not possible, due to safety concerns, to establish a Community List Entry.

Annex

List of references