25 March 2014
EMA/HMPC/321232/2012
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Panax ginseng* C.A. Meyer, radix

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Whole or cut dried root, designated white ginseng; treated with steam and then dried, designated red ginseng, of *Panax ginseng* C.A.Meyer
Herbal preparation(s)	<u>White ginseng:</u> A) Comminuted herbal substance B) Powdered herbal substance C) Dry extract (DER 2-7:1), extraction solvent ethanol 34-40% V/V D) Dry extract (DER 3-7:1), extraction solvent ethanol 40% V/V, containing 4% ginsenosides (sum of Rb_1, Rb_2, Rc, Rd, Re, Rf, Rg_1, Rg_2) E) Dry extract (DER 3-7:1), extraction solvent ethanol 57.9% V/V (=50% m/m)-60% V/V F) Dry extract (DER 3.3-5:1), extraction solvent methanol 60% V/V G) Soft extract (DER 1.7-3.2:1), extraction solvent ethanol 60%-70% V/V H) Soft extract (DER 2-6:1), extraction solvent methanol 30% V/V I) Liquid extract (DER 1: 0.8-1.2), extraction solvent ethanol 30.5% V/V (=25% m/m) – 34% V/V J) Liquid extract (DER 1:11-13.6), extraction solvent liquor wine <u>Red ginseng:</u> K) Powdered herbal substance L) Dry extract (DER 2-4.5:1), extraction solvent

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

	ethanol 60% V/V
Pharmaceutical forms	Comminuted herbal substance (herbal preparation A) as herbal tea for oral use. Herbal preparations F, K, L in solid dosage form for oral use. Herbal preparations G, H, I, J in liquid dosage form for oral use. Herbal preparation B, C, D, E in solid and liquid dosage form.
Rapporteur	R. Länger
Assessor(s)	A. Obmann, R. Länger

Table of contents

1. Introduction

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

- **Herbal substance(s)**

Ginseng radix (European Pharmacopoeia, monograph 01/2008:1523):

Ginseng radix consists of the whole or cut dried root, designated white ginseng, treated with steam and then dried, designated red ginseng, of *Panax ginseng* C.A. Meyer and contains not less than 0.40% for the sum of ginsensosides Rg1 and Rb1 (dried drug).

Constituents (Wichtl 2009, Hänsel & Sticher 2010)

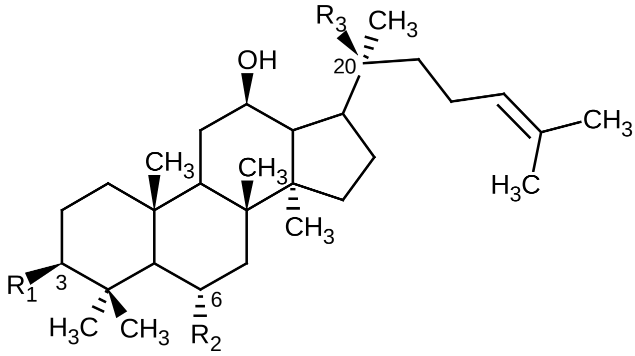
Ginsenosides:

2-3%, Triterpensaponins: Dammarane and oleanolic acid derivatives

More than 200 saponins have been isolated from ginseng species, including roots (processed and native), leaves, stems, flower buds, berries, and seeds. Regarding the chemical structure, ginseng saponins are divided into several groups. The two major groups are protopanaxadiol (PPD)-type saponins with sugar moieties attached to the C_3 and/or C_{20}, and the protopanaxatriol (PPT)-group with sugar moieties at C_6 and/or C_{20}. (**Fig. 1**). Other types include the ocotillol-type with a five-membered epoxy-ring at C_{20}, the oleanane –type with a nonsteroidal structure and the dammarane type with a modified C_{20} side chain. The nomenclature of the ginsenosides (Ra, Rb, Rc, etc.) is related to the TLC-Rf-value, whereby the polarity is decreasing from Ra to Rf, correlating to the grade of glycosylation.

So far, from the roots of *Panax ginseng* about 50 ginsenosides have been identified, mostly belonging to the neutral, bisdesmosidic type (Rb_1, Rc, Re, Rg_1), but also monodesmosides are present (Rf, Rg_2). In general the sugar chains are not branched. Except for Rg_3, Rg_2, Rh_1 and Rs_3 all ginsenosides from the unprocessed roots are of 20(S)-PPT or 20(S)-PPD-type. 20(R)-derivatives are characteristic for red ginseng and can be seen as artifacts arising during the treatment with steam. Malonylginsenosides (e.g. mRb_1, mRb_2) are only present in white ginseng, the malonyl-group is cleaved during the steam processing. (Hänsel & Sticher 2010)

Not only red and white ginseng, but also roots and leaves show considerable differences in the ginsenoside spectrum. Especially the small rootlets (“slender tails”) are rich in ginsenosides. Therefore, the qualitative and quantitative composition of and the ratio between certain ginsenosides in ginseng preparations allow conclusions about the processed plant parts and their quality.



Compound	**R_1**	**R_2**	**R_3**
Protopanaxadiol-type			
Rb_1	-O-Glc^{2}-^{1}Glc	H	-O-Glc^{6}-^{1}Glc
Rb_2	-O-Glc^{2}-^{1}Glc	H	-O-Glc^{6}-$^{1}Arabp$
Rc	-O-Glc^{2}-^{1}Glc	H	-O-Glc^{6}-$^{1}Arabf$
Rd	-O-Glc^{2}-^{1}Glc	H	-O-Glc
Compound K (metabolite)	-OH	H	-O-Glc
Protopanaxatriol-type			
Re	-OH	-O-Glc^{2}-^{1}Rha	-O-Glc
Rg_1	-OH	-O-Glc	-O-Glc
Rg_2	-OH	-O-Glc^{2}-^{1}Rha	-OH
Rf	-OH	-O-Glc^{2}-^{1}Rha	-OH
Rh_1 (metabolite)	-OH	-O-Glc	-OH

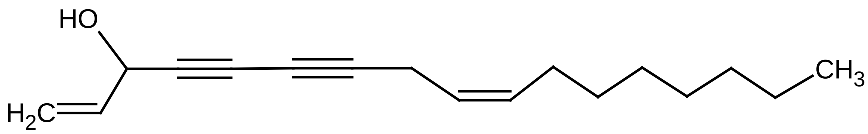
Fig. 1:Structures of main ginsenosides (Glc: β-D-glucopyranosyl, Arabp: α-L-arabinopyranosyl, Araf: α-L-arabinofuranosyl, Rha: α-L-rhamnopyranosyl)

Polysaccharides (Panaxans and Ginsenans):

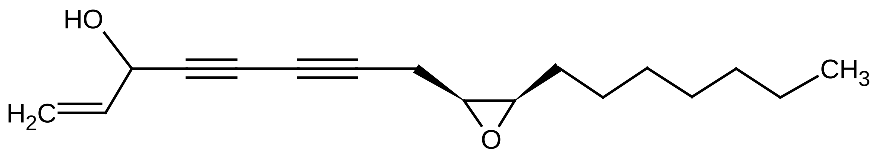
Panaxans (A-U) and ginsenans (PA, PB, S-IA and S-IIA) are polysaccharides. At present, their structures are only partly known. The main chain of panaxan A consists of α-1→6 D-glucose moieties whereas ginsenan A consists of β-1→6 D-galactose moieties.

Polyacetylenes

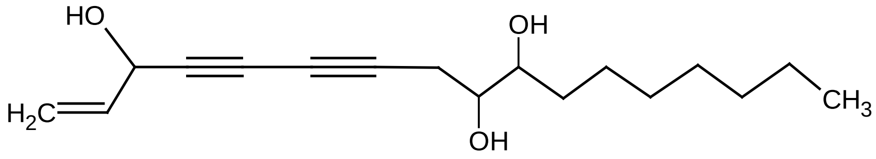
The aliphatic C_{17}-polyacetylenes panaxynol (also known as falcarinol), panaxydol, and panaxytriol have been isolated from ginseng roots and leaves (**Fig. 2**). The content of panaxynol varies from 0.002% to 0.086% in the root and reaches up to 0.03% in the leaves. The content of panaxydol varies from 0.001% to 0.2% in the roots and reaches up to 0.07% in the leaves (Washida 2003, Liu *et al.* 2007, Quian *et al.* 2009). Analyses of different parts of the root revealed that the content of panaxynol and panaxydol in the branch and fibrous roots is higher than in the main root (Liu *et al.* 2007).



(1)



(2)



(3)

Fig. 2: Structures of panaxynol (falcarinol) (1), panaxydol (2) and panaxytriol (3)

Furthermore 0.05% essential oil (citral, limonene, eremophilene, β-elemene, other monoterpenes and sesquiterpenes) phenolics, triglycerides, fatty acids, sugars, starch, pectins, amino acids, peptides, proteins and minerals are contained in the ginseng root.

- Herbal preparation(s)

Ginseng dry extract (European Pharmacopoeia, monograph 01/2013:2356):

Dry extract produced from Ginseng that contains minimum 4% of the sum of ginsenosides Rb_1, Rb_2, Rc, Rd, Re, Rf, Rg_1 and Rg_2, expressed as ginsenoside Rb_1 ($C_{54}H_{92}$, O_{23}; M_r1109) (dried extract). The extract is produced from the herbal drug by a suitable procedure using a hydroalcoholic solvent equivalent in strength to ethanol (35-90% V/V).

For all other herbal preparations see section 2.

- 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.

The request for information exchange concerning ginseng radix preparations revealed that several ginseng preparations in combination with other herbal substances/preparations, e.g. ginkgo, or vitamins and minerals are on the market. However, such combinations are not subject of this assessment report.

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

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

Member State	Regulatory Status				Comments
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Additionally many products in combination with vitamins and minerals as food supplements
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Additionally one combination product with Menyanthes trifoliata and ascorbic acid
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	No combination products on the market, no “German standard marketing authorisations”
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Additionally one combination product with vitamins, minerals, micronutrients
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Food supplements; No herbal medicinal products
Latvia	☒ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Authorised products, Food supplements; Combination products (ginkgo)
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☒ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Additionally food supplements on the market
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

Member State	Regulatory Status				Comments
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Traditional use: Registration and MA…not clear
Sweden	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

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

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

1.3. Search and assessment methodology

Pubmed, Toxnet: search date 21.9.2011, search terms: Ginseng, Panax ginseng, Ginsenoside, Panaxans, Panaxadiol, Panaxatriol; search date 18.1.2013, search terms: panaxynol, falcarinol, “ginseng and allergy”, “Araliaceae and allergy”

Other sources: ESCOP Monographs, The complete German Commission E monographs, Madaus, Panax Ginseng Natural Standard Database

Publications in other languages than English or German (at least abstract in English or German available) were precluded from assessment.

2. Data on medicinal use

2.1. Information on period of medicinal use in the Community

Ginseng root has been in medicinal use for thousands of years in Eastern Asia (Korea, China, Japan) as a tonic, for the treatment of general weakness, cold extremities, lack of appetite, weakness, and cachexia after long duration of illness, anxiety accompanied with heart palpitation and insomnia, impotence and infertility in women, and cardiac insufficiency. It is one of the most important medicinal products in traditional Chinese, Mongolian and other East Asian medicine. Ginseng root (“rén shēn”) is referred in the Chinese Herbal Medicine Materia Medica (Bensky *et al.* 2004) as an herb which powerfully tonifies the “primal qi” and the “qi of all organs”, especially that of the lungs and spleen. It generates fluids, quiets the spirit, and strengthens the resolve. Through its tonification of “qi” it generates blood, encourages blood flow, and controls bleeding. The properties according to TCM ascribed to ginseng root are sweet, slightly bitter, and slightly warm. Therefore, ginseng root is used for extreme collapse of the “qi” or abandoned conditions that manifest in shallow breathing, shortness of breath, cold limbs, profuse sweating, and weak pulse. These conditions can occur after loss of blood, overly profuse sweating, or other problems related to severe fluid loss. In such cases ginseng is used as a single herb. Furthermore ginseng root is used in special preparations in combination with other ingredients, e.g. ‟shēng mài sǎn” containing Schisandrae fructus, Ophiopogonis radix and Ginseng radix. It is regarded irreplaceable when disorders are severe or in need of immediate relief. According to the Chinese Herbal Materia Medica doses of 3-9 g are applied, usually cooked separately in a double boiler with the resulting liquid added to the strained decoction of other herbs (in case of a special formula). When the drug is taken directly as a powder, the dosage is 0.5-1 g. In emergencies up to 30 g can be used, divided into multiple doses. In general, distinction is made between white ginseng ("bái rén shēn"), red ginseng ("hóng shēn"), ginseng neck ("rén shēn lú") and ginseng leaf (rén shēn yè). Furthermore, products are distinguished based on their origin, method of processing, or root parts used. The root of *Panax quinquefolius* can be used as a substitute if the use of *Panax ginseng* is indicated but its warming quality is not wanted (Bensky *et al.* 2004). In 1610 the herbal substance came to Europe via the Netherlands and became generally known as "Pentao". Also in Europe ginseng was regarded as most valuable and a very expensive herbal substance even at the beginning of the 19th century (Madaus 1938). The traditional use of the comminuted herbal substance for tea preparation is documented in pharmaceutical standard references (e.g. List & Hörhammer 1977, British Herbal Pharmacopoeia 1983)

Each of the following mentioned preparations is authorised in the respective member state. Most of the preparations are marketed since 1976. Today, most preparations are used as a tonic in case of tiredness, weakness and decreased mental and physical capacity (for details concerning approved indications see the following tables).

Austria

No	Preparation	MA	Dosage form	Posology	Indication
1.	Powdered herbal substance (Red Ginseng), standardised to 6% ginsenosides	1996	Hard capsules	Once daily 2-3 capsules, up to 2 times daily 3 capsules (300 mg powdered herbal substance per capsule) As a cure: For the first two months 2 times daily 2-3 capsules. A duration of use of 6 months is recommended.	Asthenia, such as lack of concentration, fatigue, weakness, tiredness, lack of vitality or in convalescence
2.	Dry extract from Ginseng Radix, DER 5:1 (3-7:1), standardised to 4% ginsenosides (sum of Rb_1, Rb_2, Rc, Rd, Re, Rf, Rg_1, Rg_2), extraction solvent 40% EtOH V/V	1981	Soft capsule Oral liquid	Once daily 2 capsules (100 mg dry extract per capsule) Once daily 15 ml of the oral liquid (15 ml contain 140 mg dry extract)	Exhaustion, fatigue lack of concentration, lack of vitality and during convalescence. To strengthen the immune system

Additional information concerning posology:

According to the approved SmPC preparation 1 is intended for oral use in adults.

According to the approved SmPCs preparation 2 is intended for oral use in adults. Duration of use of 8-12 weeks is recommended. Before re-administering ginseng-preparations a break of 1 month is recommended.

Belgium

No	Preparation	MA	Dosage form	Posology	Indication
1	Radix extract G115	2000	Soft capsules	Adults: 2 x 100 mg extract Adolescents from 12 years on: 1x 100 mg	Symptomatic treatment of fatigue, after underlying illness has been excluded
2	Radix, powdered, minimal 8% and max. 10% of total ginsenosides expressed as ginsenoside Rg1	1997 up to 2010	Hard capsules	Adults & Adolescents from 12 years on: 3 -4 x 300 mg a day	Symptomatic treatment of fatigue, after underlying illness has been excluded

Additional information regarding food supplements submitted by the Belgian National Competent Authority:

A query (“Panax ginseng”) resulted in a list of 854 food supplements, including a number of combination products. The information is not very conclusive as the herbal substance/preparation is not always (almost never) mentioned on the list and can therefore not be further characterized. Data on posology is not available. A lot of products include a reference to “energy” in their name, and refer to male sexual performance enhancement (aphrodisiac) or immune support. Notifications go back to 1990.

Denmark

No	Preparation	MA	Dosage form	Posology	Indication
1.	Dry extract from Ginseng Radix, DER 5:1 (3-7:1), standardised to 4% ginsenosides (sum of Rg1, Re, Rb1, Rc, Rb2, Rd), extraction solvent 40% EtOH V/V	2000	Soft capsules	2 capsules in the morning or 1 capsule in the morning and 1 capsule in the middle of the day. Dosage can be increased to 4 capsules per day in the first 5 days in special situations (100 mg dry extract per capsule)	Herbal medicinal product in exhaustion fatigue and at convalescence; can be tried in lack of concentration in middle aged and elderly when other causes to the condition have been excluded
2.	Powdered herbal substance	1994	Hard gelatine capsules	2 capsules in the morning or 1 capsule in the morning and 1 capsule in the middle of the day. Dosage can be increased to 4 capsules per day in the first 5 days in special situations (300 mg powdered herbal substance per capsule)	Herbal medicinal product in exhaustion, fatigue and at convalescence; can be tried in lack of concentration in middle aged and elderly when other causes to the condition has been excluded

Additional comments: Many products with ginseng are sold as food supplements – many in combination with vitamins and minerals. Preparation 1 achieved the marketing authorisation in 2000 but is on the market since 1990.

Additional information concerning posology: According to the approved SmPCs preparations 1 and 2 are intended for oral use in adults. A maximum duration of 3 months is followed by a pause in treatment of 1 month before the preparations are re-administered.

France

No	Preparation	MA	Dosage form	Posology	Indication
1.	Powdered herbal substance	1981	Hard capsule	2 hard capsules 2 times daily, up to 5 hard capsules, if necessary (390 mg of powder/capsule)	Traditionally used in functional asthenia

2.	Dry extract, DER 3-7:1, extraction solvent EtOH 96% V/V	1988	Soft capsule	2-4 soft capsules per day (100 mg dry extract per capsule)	Traditionally used in functional asthenia
3.	Dry extract, DER 3-7:1, extraction solvent EtOH 96% V/V	1997	Oral solution	15 ml of oral solution per day (934 mg of extract/100 ml)	Traditionally used in functional asthenia
4.	Powdered herbal substance	1976	Hard capsule	1 hard capsule 3 times daily (250 mg powdered herbal substance/capsule)	Traditionally used in functional asthenia
5.	Powdered herbal substance	1976	Hard capsule	2 hard capsules 2 times daily (500 mg powdered herbal substance/capsule)	Traditionally used in functional asthenia

Additional information concerning posology: Due to the content in saponins, it is mentioned in the French “Cahiers de l’Agence N° 3” that the daily dose should not be more than 2 g and the maximum duration of treatment should be 3 months.
Additional comment: There exists only one combination product (with *Menyanthes trifoliata* L. and ascorbic acid).

Germany

No	Preparation	MA	Dosage form	Posology	Indication
1.	Ginseng radix, powder	At least since 1976	Hard capsule	3 times daily 1 capsule containing 350 mg Ginseng radix powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
2.	Dry extract from Ginseng radix, DER 3-4.5:1, extraction solvent ethanol 30% (m/m)	At least since 1976	Pastille	3 times daily 1 containing 100 mg dry extract (in case of particular stress up to 4 times 1	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
3.	Dry extract from Ginseng radix, DER 3-4.5:1, extraction solvent ethanol 30% (m/m)	At least since 1976	Coated tablet	2 times daily 2 containing 125 mg dry extract	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in

					concentration as well as during convalescence.
4.	Dry extract from Ginseng radix, DER 3-4.5:1, extraction solvent ethanol 30% (m/m)	At least since 1976	Pastille	3 times daily 1 containing 100 mg dry extract (in case of particular stress up to 4 times 1	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
5.	Ginseng radix, powder	At least since 1976	Hard capsule	3 times daily 1 capsule containing 350 mg Ginseng radix powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
6.	Ginseng radix, powder	At least since 1976	Hard capsule	2 times daily 2 containing 350 mg Ginseng radix each	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.
7.	Soft extract from Ginseng radix, DER 2-6:1, extraction solvent methanol 30% V/V	At least since 1976	Oral liquid	2 times daily 15 ml oral liquid (100 ml contains 1.4651g extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
8.	Ginseng radix, powder	At least since 1976	Hard capsule	3 times daily 1 capsule containing 350 mg Ginseng radix powder	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.
9.	Liquid extract from Ginseng radix, DER 1:1, extraction solvent ethanol 34% V/V	At least since 1976	Oral liquid	2 times daily 20 ml oral liquid (20 ml contain 1 ml extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
10.	Ginseng radix, powder	At least since 1976	Oral liquid	1 time daily 15 ml oral liquid (corresponding to 1.2 g Ginseng radix)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.

11.	Dry extract from Ginseng radix, DER 3.5-4.5:1, extraction solvent ethanol 34% V/V	At least since 1976	Herbal instant tea	1 time daily 3 g granules dissolved in a cup of hot water (100g granules contain 12 g extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
12.	Ginseng radix, powder	At least since 1976	Powder	2 times daily 1 g Ginseng radix powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
13.	Ginseng radix, powder	At least since 1976	Hard capsule	2 times daily 1 containing 500 mg Ginseng radix powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
14.	Dry extract from Red Ginseng radix, DER 3.5-4.5:1), extraction solvent ethanol 60% V/V	At least since 1976	Powder for oral solution	1 time daily 1 sachet of powder containing 0.475 g dry extract	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
15.	Ginseng radix, powder	At least since 1976	Powder	3 times daily 500 mg Ginseng radix powder	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.
16.	Dry extract from Ginseng radix, DER 6-7:1, extraction solvent ethanol 30% (m/m)	At least since 1976	Soft capsule	3 times daily 1 containing 90 mg dry extract	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.
17.	Dry extract from Ginseng radix, DER 3.2-4:1, extraction solvent ethanol 60% V/V	At least since 1976	Oral liquid	2 times daily 30 ml liquid containing 205.8 mg dry extract	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
18.	Red Ginseng radix, powder	At least since	Hard capsule	3 times daily 2 containing 300 mg Ginseng radix powder each	As a tonic in case of tiredness and weakness and decreased mental and

		1976			physical capacity as well as in concentration.
19.	Liquid extract from Ginseng radix, DER 1:0.8-1.2, extraction solvent ethanol 25% (m/m)	At least since 1976	Oral liquid	1 time daily 3.3 ml liquid (100 ml=116 g contain 38.28 g liquid extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
20.	Dry extract from Red Ginseng radix, DER 2.2-3.8:1, extraction solvent ethanol 60% V/V	At least since 1976	Herbal instant tea	2 times daily 2.5 g granules dissolved in a cup of 100 ml hot water (1 g granules contains 72 mg dry extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
21.	Dry extract from Red Ginseng radix, DER 3-4:1, extraction solvent ethanol 60% V/V	At least since 1976	Hard capsule	1 time daily 1 containing 500 mg dry extract	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
22.	Red Ginseng radix, powder	At least since 1976	Tablet	3 times daily 2 containing 300 mg dry extract each	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
23.	Dry extract from Red Ginseng radix, DER 3-4:1, extraction solvent ethanol 60% V/V	At least since 1976	Hard capsule	1 time daily 1 containing 500 mg dry extract	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
24.	Ginseng radix, powder	At least since 1976	Hard capsule	2 times daily 2 containing 250 mg Ginseng radix powder each	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.

25.	Dry extract from Ginseng radix, DER 3-7:1, extraction solvent ethanol 60% V/V	At least since 1976	Oral liquid	2-4 times daily 15 ml liquid (100 ml contain 653.34 mg dry extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
26.	Dry extract from Ginseng radix, DER 3-7:1, extraction solvent ethanol 40% V/V	At least since 1976	Soft capsule	2 times daily 1 containing 100 mg dry extract (up to 4 times 1 is possible)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
27.	Ginseng radix, powder	At least since 1976	Hard capsule	2-3 times daily 2 containing 250 mg Ginseng radix powder each	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.
28.	Dry extract from Ginseng radix, DER 3-4.5:1, extraction solvent ethanol 30% (m/m)	At least since 1976	Oral liquid	2 times daily 10-15 ml liquid (500 ml contain 7.5 g dry extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
29.	Ginseng radix, powder	At least since 1976	Hard capsule	3 times daily 1 capsule containing 350 mg Ginseng radix powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
30.	Dry extract from Ginseng radix, DER 2.1-3.9:1, extraction solvent ethanol 40% V/V	At least since 1976	Hard capsule	2 times daily 1-2 containing 166,7 mg dry extract each	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
31.	Soft extract from Ginseng radix, DER 1.7-2.9:1, extraction solvent ethanol 70%	At least since 1976	Soft extract	2 times daily 0.3-0.35 g soft extract	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
32.	Ginseng radix, powder	At least	Hard capsule	2 times daily 2 containing 350 mg	As a tonic in case of tiredness and

		since 1976		dry extract each	weakness and decreased mental and physical capacity as well as in concentration.
33.	Dry extract from Ginseng radix, DER 3-4:1, extraction solvent ethanol 60% V/V	At least since 1976	Hard capsule	2-3 times daily 1 containing 175 mg dry extract	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
34.	Liquid extract from Ginseng radix, DER 1:1, extraction solvent ethanol 34% V/V	At least since 1976	Oral liquid	2 times daily 20 ml liquid (20 ml contain 1 ml liquid extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
35.	Ginseng radix, powder	At least since 1976	Hard capsule	Up to 3 times daily 2 containing 180 mg Ginseng radix powder each	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
36.	Dry extract from Ginseng radix, DER 3-7:1, extraction solvent ethanol 40% V/V	At least since 1976	Oral liquid	1 time daily (in the morning) 15 ml liquid containing 200 mg dry extract (up to 30 ml per day is possible)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
37.	Liquid extract from Ginseng radix, DER 1:1, extraction solvent ethanol 34% m/m	At least since 1976	Oral liquid	1-2 times daily 5 ml liquid (100 g=100.75 ml liquid contain 25 g liquid extract)	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.
38.	Liquid extract from Ginseng radix, DER 1:1, extraction solvent ethanol 34% V/V	At least since 1976	Oral liquid	1-2 times daily 5 ml liquid (100 g=100 ml liquid contain 25 g liquid extract)	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.
39.	Extract from Ginseng radix, DER 1:11-13.6, extraction solvent liquor wine	At least since 1976	Oral liquid	1 time daily 20 ml liquid (100 g=96 ml liquid contain 95.2 g extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in

					concentration.
40.	Dry extract from Ginseng radix, DER 3-7:1, extraction solvent ethanol 60% V/V	At least since 1976	Oral liquid	2-4 times daily 15 ml liquid (100 ml contain 653.34 mg dry extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
41.	Dry extract from Ginseng radix, DER 3-7:1, extraction solvent ethanol 60% V/V	At least since 1976	Oral liquid	2-4 times daily 15 ml liquid (100 ml contain 653.34 mg dry extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
42.	Dry extract from Ginseng radix, DER 3.6-5.5:1, extraction solvent ethanol 50% (m/m)	At least since 1976	Soft capsule	3 times daily 1 containing 100 mg dry extract	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
43.	Dry extract from Ginseng radix, DER 3-4.5:1, extraction solvent ethanol 30% (m/m)	At least since 1976	Oral liquid	2 times daily 15 ml liquid (100 ml liquid contain 1.5 g dry extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration as well as during convalescence.
44.	Dry extract from Ginseng radix, DER 3-5:1, extraction solvent ethanol 36% V/V	At least since 1976	Soft capsule	2 times daily 2 containing 100 mg dry extract each	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
45.	Dry extract from Ginseng radix, DER 3.6-5.5:1, extraction solvent ethanol 50% (m/m)	At least since 1976	Soft capsule	2 times daily 1 containing 220 mg dry extract	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
46.	Liquid extract from Ginseng radix, DER 1:1, extraction solvent	At least since	Oral liquid	1-2 times daily 15 ml liquid (100 g liquid contain 6.6 g liquid extract)	For the strengthening in case of tiredness and weakness and decreased

	ethanol 34% V/V	1976			mental and physical capacity.
47.	Dry extract from Ginseng radix, DER 3-5:1, extraction solvent ethanol 36% V/V	At least since 1976	Soft capsule	2 times daily 2 containing 100 mg dry extract each	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
48.	Ginseng radix, powder	At least since 1976	Hard capsule	2 times daily 2 containing 250 mg Ginseng radix powder each	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
49.	Dry extract from Ginseng radix, DER 3-4:1, extraction solvent ethanol 60% V/V	At least since 1976	Oral liquid	3 times daily 20 ml liquid (100 ml liquid contain 0.665 g dry extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
50.	Dry extract from Ginseng radix, DER 3-4.5:1, extraction solvent ethanol 30% (m/m)	At least since 1976	Coated tablet	2 times daily 1-2 containing 125 mg dry extract each	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
51.	Ginseng radix, powder	At least since 1976	Powder	4-8 times daily 250 mg Ginseng radix powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
52.	Dry extract from Ginseng radix, DER 3.3-5:1, extraction solvent methanol 60%	At least since 1976	Coated tablet	3 times daily 1 containing 120 mg dry extract	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
53.	Ginseng radix, powder	At least since 1976	Hard capsule	2 times daily 2 containing 250 mg Ginseng radix powder each	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in

					concentration.
54.	Soft extract from Ginseng radix, DER 2.5-3.2:1, extraction solvent ethanol 60% V/V	At least since 1976	Syrup	1 time daily 0.88 g syrup pure or dissolved in a cup of hot water (100 g syrup contain 50 g soft extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
55.	Liquid extract from Ginseng radix, DER 1:1, extraction solvent ethanol 34% V/V	At least since 1976	Oral liquid	2 times daily 5-10 ml liquid (10 ml liquid contain 1 g liquid extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
56.	Dry extract from Ginseng radix, DER 3-4.5:1, extraction solvent ethanol 30% (m/m)	At least since 1976	Oral liquid	1-2 times daily 15 ml liquid (100 ml liquid contain 1.5 g dry extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration as well as during convalescence, after recovering from illness as well as during convalescence.
57.	Red Ginseng radix, powder	1999	Hard capsule	1 time daily 4 containing 300 mg Ginseng radix powder each	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
58.	Dry extract from Ginseng radix, DER 3.5-4.5:1, extraction solvent ethanol 34% V/V	1999	Herbal instant tea	1 time daily 1 sachet containing 0.475 g dry extract dissolved in a cup of hot water	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.
59.	Extract from Ginseng radix, DER 1:16-18, extraction solvent ethanol 15% (m/m)	At least since 1990	Oral liquid	2 times daily 15 ml liquid (100 g=101.5 ml liquid contain 99.348 g extract)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.

	Traditional use				Indication
60.	Red Ginseng radix in slices	At least since 1976	Herbal parts	3 times daily 1 slice of root (for chewing and swallowing	Traditional herbal medicinal product to improve the general condition. The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.

Additional information concerning posology: All preparations are intended for oral use in adults and adolescents over 12 years. In general, an application is recommended for 3 months. Because of the continuing effects of ginseng preparations before re-administering a dose of 1 month break is recommended.
Additional comments: No German Standard Marketing Authorisations, neither for the single active ingredient nor for combination products.

Ireland

No	Preparation	MA	Dosage form	Posology	Indication
1.	Standardised dry extract, DER 1.3-3:1; 4% w/w Ginsenosides, extraction solvent EtOH 40% (m/m or V/V?)	1984	Soft capsule	2 capsules daily (100 mg dry extract per capsule),	As an adjunct in management of patients with impaired general health or those who are convalescent
2.	Standardised dry extract, DER 1.3-3:1; 4% w/w Ginsenosides, extraction solvent EtOH 40% (m/m or V/V?)	1994	Oral solution	15 ml daily (each 15 ml solution contains 140 mg dry extract);	As an adjunct in management of patients with impaired general health or those who are convalescent

Additional information concerning posology: Preparations 1 and 2 are intended for duration of use of 8-12 weeks and not recommended for children.

Additional comment: One combination product is available – multi-vitamin/mineral supplement containing ginseng (same extract as above mentioned preparations)

Italy

According to the information of the Italian Medicines Agency at present no herbal medicinal products containing Ginseng are licensed in Italy. Ginseng radix is included in the list of ingredients allowed in food supplements, published on the website of the Italian Ministry of health, with reference to the following effects: mental and psychological stress, human body adapting capacity, carbohydrates metabolism and antioxidant.

Latvia

Only a combination with Ginkgo is on the market.

Poland

No	Preparation	MA	Dosage form	Posology	Indication
1.	Ginseng G115 extract, standardised and highly concentrate, DER native 3-7:1, extraction solvent EtOH 40% V/V	1990	Oral liquid	15 ml (containing 9.3 mg extract) a day	As tonic and strengthening agent in tiredness and weakness, in decreased physical efficiency and in convalescence
2.	Ginseng radix	1999	Herbal tea	2 g once daily	Traditionally in tiredness, weakness, decreased physical efficiency and reduction of concentration
3.	Ginseng tincture (1:5), extraction solvent ethanol 70% V/V	2002	Oral liquid	2.5 ml 2 times daily	Traditionally as strengthening agent in tiredness and weakness, in reduction of concentration and in convalescence In geriatrics to improve general feeling

Portugal

No	Preparation	MA	Dosage form	Posology	Indication
1.	Ginseng G115 extract, standardised and highly concentrate, DER 5:1, extraction	1995	Soft capsule	2 capsules at breakfast or one for breakfast and another for lunch.	Increases the physical and intellectual abilities in situations of fatigue, weakness and exhaustion or during convalescence. Helps the body to resist

	solvent EtOH 40% V/V				stressful situations and reinforces the defenses against disease.
2.	Ginseng G115 extract, standardised and highly concentrate, DER 5:1, extraction solvent EtOH 40% V/V	1995	Oral solution	1 measuring cup (15 ml, one tablespoon full) a day, preferably for breakfast.	No information but probably same indication as for preparation 1

Assessor's comment: *The preparations are referred to as "G 115". Therefore, see also Austria preparation 2, Denmark preparation 1.*

Additional information concerning posology: In situations of severe stress the daily dose may be increased 4 capsules during the initial treatment period (preparation 1)/ up to 30 ml during the initial period of treatment (preparation 2).

Spain

No	Preparation	MA	Dosage form	Posology	Indication
1.	Dry extract, DER 5:1, 5-7% ginsenosides calculated as ginsenoside Rg1, extraction solvent 70% V/V	2001	Tablets	2 tablets per day (100 mg of standardised dry extract per tablet	Symptomatic treatment of asthenia such as fatigue, weakness
2.	Dry extract, DER 4-6:1, 5-7% ginsenosides, extraction solvent EtOH 50% V/V	2007	Soft capsules	1 or 2 soft capsules per day (100 mg of standardised dry extract per capsule)	Symptomatic treatment of asthenia such as fatigue, weakness
3.	Powdered herbal substance	1987 1996	Hard capsules Tablets	3-5 capsules/tablets per day (300 mg powdered herbal substance per capsule/tablet)	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness

Additional information concerning posology: Duration of use no longer than 8 weeks

Sweden

No	Preparation	MA	Dosage form	Posology	Indication
1.	*Panax ginseng* C.A. Meyer, radix, standardised dry extract (G115), DER 5:1 (3-7:1) Extraction solvent: ethanol 40%	1978 2012	Capsules, soft	1-2 capsules (100 mg of extract per capsule) daily at breakfast/lunch	Traditional herbal medicinal product used as a tonic in case of decreased performance such as fatigue and sensation of weakness.
2.	*Panax ginseng* C.A. Meyer, radix, standardised dry extract (G115), DER 5:1 (3-7:1) Extraction solvent: ethanol 40%	1978 2012	Oral solution	10 ml (1 ml 9,3 mg extract) 1-2 times daily at breakfast/lunch	Traditional herbal medicinal product used as a tonic in case of decreased performance such as fatigue and sensation of weakness.
3.	*Panax ginseng* C.A. Meyer, radix, standardised dry extract (G115), DER 5:1 (3-7:1) Extraction solvent: ethanol 40%	1978 2012	Capsules soft	1 capsule (40 mg of extract per capsule) daily at breakfast	Traditional herbal medicinal product used as a tonic in case of decreased performance such as fatigue and sensation of weakness.
4.	*Panax ginseng* C.A. Meyer, radix, standardised dry extract (G115), DER 5:1 (3-7:1) Extraction solvent: ethanol 40%	2001 2012	Film-coated tablets	1 tablet (100 mg of extract per tablet) daily at breakfast	Traditional herbal medicinal product used as a tonic in case of decreased performance such as fatigue and sensation of weakness.
5.	*Panax ginseng* C.A. Meyer, radix, standardised dry extract (G115), DER 5:1 (3-7:1) Extraction solvent: ethanol 40%	2006 2012	Effervescent tablets	1 effervescent tablet (40 mg of extract per tablet) daily at breakfast	Traditional herbal medicinal product used as a tonic in case of decreased performance such as fatigue and sensation of weakness.

Additional information: The herbal preparation is in medicinal use at least since 1978. In 2012 the products were reclassified as traditional herbal medicinal products according to Dir. 2001/83 as amended.

Consolidated list of herbal preparations fulfilling the criteria of at least 30 years of medicinal use as defined in Dir. 2001/83 as amended:

White ginseng:

A) Comminuted herbal substance as decoction for oral use:

According to British Herbal Pharmacopoeia (1983), Hagers Handbook (List & Hörhammer 1977, Blaschek *et al.* 2008)

Poland preparation 2

B) Powdered herbal substance:

Germany: Preparations 1, 5, 6, 8, 10, 12, 13, 15, 24, 27, 29, 32, 35, 48, 51, 53

France: Preparations 1, 4, 5

C) Dry extract (DER 2-7:1), extraction solvent ethanol 34-40% V/V

Germany: Preparations 2, 3, 4, 11, 16, 26, 28, 30, 36, 43, 44, 47, 50, 56, 58

D) Dry extract (DER 3-7:1), extraction solvent ethanol 40% V/V, containing 4% ginsenosides (sum of Rb_1, Rb_2, Rc, Rd, Re, Rf, Rg_1, Rg_2)

Austria: Preparation 2

Belgium: Preparation 1

Denmark: Preparation 1

Ireland: Preparations 1, 2

Poland: Preparation 1

Portugal: Preparations 1, 2

Sweden: Preparations 1, 2, 3, 4, 5

Assessors comment:

This dry extract is often referred as special extract G115 and is marketed in several member states. However, the DER has been reported differently by national competent authorities depending on whether the addition of excipients had been considered for the establishment of the DER or not.

E) Dry extract (DER 3-7:1), extraction solvent ethanol 57.9% V/V (= 50% m/m) – 60% V/V

Germany: Preparations 17, 25, 33, 40, 41, 42, 45, 49

F) Dry extract (DER 3.3-5:1), extraction solvent methanol 60% V/V

Germany: Preparation 52

G) Soft extract (DER 1.7-3.2:1), extraction solvent ethanol 60%-70% V/V

Germany: Preparations 31, 54

H) Soft extract (DER 2-6:1), extraction solvent methanol 30% V/V

Germany: Preparation 7

I) Liquid extract (DER 1:0.8-1.2), ethanol 30.5% V/V (= 25% m/m) – 34% V/V

Germany: Preparations 9, 19, 34, 37, 38, 46, 55

J) Liquid extract (DER 1:11-13.6), extraction solvent liquor wine

Germany: Preparation 39

Red Ginseng:

K) Powdered herbal substance:

Germany: Preparations 18, 22

L) Dry extract (DER 2-4.5:1), extraction solvent ethanol 60% V/V

Germany: Preparations 14, 20, 21, 23

<u>Herbal preparations not included in the monograph:</u>

- Dry extract, DER 5:1, extraction solvent ethanol 70%, 5-7% ginsenosides

  Spain preparation 1

  The herbal preparation is on the market since 2001. Published clinical data are not of sufficient quality in order to propose well-established use.

- Dry extract, DER 4-6:1, extraction solvent ethanol 50%, 5-7% ginsenosides

  Spain preparation 2

  The herbal preparation is on the market since 2007 and does neither fulfil the criteria for well-established nor for traditional use.

- Dry extract, DER 3-7:1, extraction solvent ethanol 96%

  France preparations 2 and 3

  The herbal preparations are on the market since 1988 and 1997 respectively and fulfil neither the criteria for well-established nor for traditional use.

- Liquid extract, DER 1:16-18, extraction solvent ethanol 15% m/m

  Germany preparation 59

  The herbal preparation is on the market since 1990 and does neither fulfil the criteria for well-established nor for traditional use.

- Powdered herbal substance, standardised to 8-10% ginsenosides

  Belgium preparation 2

  The herbal preparation is on the market since 1997 and does neither fulfil the criteria for well-established nor for traditional use.

- Tincture (1:5), extraction solvent ethanol 70% V/V

  Poland preparation 3

  The herbal preparation is on the market since 1999 and does neither fulfil the criteria for well-established nor for traditional use.

- Powdered herbal substance (Red ginseng), standardised to 6% ginsenosides

  Austria preparation 1

  The herbal preparation is on the market since 1996 and does neither fulfil the criteria for well-established nor for traditional use.

- Comminuted herbal substance (Red ginseng)

  Germany preparation 60

  Although the herbal preparation itself is in medicinal use since at least 30 years with at least 15 years in the EU, the information regarding the posology (3 times daily 1 slice of root for chewing and swallowing) is not precise enough for inclusion in the monograph.

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

Indications of herbal preparations fulfilling the criteria of traditional use as defined in Dir. 2001/83 as amended:

A) Comminuted herbal substance as decoction for oral use:

British Herbal Pharmacopoeia (1983): Neurasthenia, Neuralgia, Insomnia, Hypotonia

B) Powdered herbal substance:

Germany:

Wording 1: As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.

Wording 2: For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.

France: Traditionally used in functional asthenia

C) Dry extract (DER 2-7:1), extraction solvent ethanol 34-40% V/V

Germany:

Wording 1: As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.

Wording 2: For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.

D) Dry extract (DER 3-7:1), extraction solvent ethanol 40% V/V, containing 4% ginsenosides (sum of Rb_1, Rb_2, Rc, Rd, Re, Rf, Rg_1, Rg_2)

Austria: In case of exhaustion, fatigue, lack of concentration, lack of vitality and during convalescence. To strengthen the immune system

Belgium: Symptomatic treatment of fatigue, after underlying illness has been excluded

Denmark: Herbal medicinal product in exhaustion fatigue and at convalescence; can be tried in lack of concentration in middle aged and elderly when other causes to the condition have been excluded

Ireland: As an adjunct in management of patients with impaired general health or those who are convalescent

Poland: As tonic and strengthening agent in tiredness and weakness, in decreased physical efficiency and in convalescence

Portugal: Increases the physical and intellectual abilities in situations of fatigue, weakness and exhaustion or during convalescence. Helps the body to resist stressful situations and reinforces the defences against disease.

E) Dry extract (DER 3-7:1), extraction solvent ethanol 57.9% V/V (= 50% m/m) – 60% V/V

Germany: As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.

F) Dry extract (DER 3.3-5:1), extraction solvent methanol 60% V/V

Germany: As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.

G) Soft extract (DER 1.7-3.2:1), extraction solvent ethanol 60%-70% V/V

Germany: As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.

H) Soft extract (DER 2-6:1), extraction solvent methanol 30% V/V

Germany: As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.

I) Liquid extract (DER 1:0.8-1.2), ethanol 30.5% V/V (= 25% m/m) – 34% V/V

Germany:

Wording 1: As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.

Wording 2: For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.

J) Liquid extract (DER 1:11-13.6), extraction solvent liquor wine

Germany: As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.

Red Ginseng:

K) Powdered herbal substance:

Germany: As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.

L) Dry extract (DER 2-4.5:1), extraction solvent ethanol 60% V/V

Germany: As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.

Proposed indication: Since ginseng shows similarities to *Eleutherococcus senticosus* regarding its therapeutic properties the indication should be worded as follows: Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.

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

The data on posology are taken from literature as well as nationally authorised or registered medicinal products which are at least since 30 years in medicinal use.

Posology:

A) Comminuted herbal substance as decoction for oral use:

Single dose: 1000 – 2000 mg (British Herbal Pharmacopoeia 1983, Blaschek *et al.* 2008)

Daily dose: 2000 – 6000 mg (Blaschek *et al.* 2008)

Dosage frequency: 3 times daily (British Herbal Pharmacopoeia 1983)

B) Powdered herbal substance:

Single dose: 250 – 1200 mg

Daily dose: 600 – 2000 mg

Dosage frequency: once daily (1200 mg), 2 -8 times daily

C) Dry extract (DER 2-7:1), extraction solvent ethanol 34-40% V/V

Single dose: 90 – 360 mg

Daily dose: 200 – 670 mg

Dosage frequency: 1 – 4 times daily

D) Dry extract (DER 3-7:1), extraction solvent ethanol 40% V/V, containing 4% ginsenosides (sum of Rb_1, Rb_2, Rc, Rd, Re, Rf, Rg_1, Rg_2)

Single dose: 40-200 mg

Daily dose: 40-200 mg (can be increased up to 600 mg in the first 5 days in special situations)

Dosage frequency: 1-2 times daily

E) Dry extract (DER 3-7:1), extraction solvent ethanol 57.9% V/V (= 50% m/m) – 60% V/V

Single dose: 98 – 220 mg

Daily dose: 196 – 525 mg

Dosage frequency: 2 – 4 times daily

F) Dry extract (DER 3.3-5:1), extraction solvent methanol 60% V/V

Single dose: 120 mg

Daily dose: 360 mg

Dosage frequency: 3 times daily

G) Soft extract (DER 1.7-3.2:1), extraction solvent ethanol 60%-70% V/V

Single dose: 300 - 440 mg

Daily dose: 440 – 700 mg

Dosage frequency: once (440 mg) or 2 times daily

H) Soft extract (DER 2-6:1), extraction solvent methanol 30% V/V

Single dose: 219.8 mg

Daily dose: 439.6 mg

Dosage frequency: 2 times daily

I) Liquid extract (DER 1:0.8-1.2), ethanol 30.5% V/V (= 25% m/m) – 34% V/V

Single dose: 500 mg – 1250 mg

Daily dose: 990 mg – 2500 mg

Dosage frequency: 1-2 times daily

J) Liquid extract (DER 1:11-13.6), extraction solvent liquor wine

Single dose: 19.4 ml

Daily dose: 19.4 ml

Dosage frequency: once daily

Red Ginseng:

K) Powdered herbal substance:

Single dose: 600 mg

Daily dose: 1800 mg

Dosage frequency: 3 times daily

L) Dry extract (DER 2-4.5:1), extraction solvent ethanol 60% V/V

Single dose: 180 – 500 mg

Daily dose: 360 – 500 mg

Dosage frequency: once (475 mg or 500 mg) or 2 times daily

Route of administration:

All herbal preparations: oral use

Age limits:

Austria, Denmark: adults

Germany: adolescents and adults

Proposed age limit for the monograph: Adults and elderly

Duration of use:

Austria: 8-12 weeks, then minimum break of 1 month

Denmark, Germany: 3 months, then minimum break of 1 month

Spain: not longer than 8 weeks

France: maximum duration of treatment 3 months

Proposed duration of use for the monograph: Duration of use up to 3 months. If the symptoms persist for more than 2 weeks during the use of the medicinal product, a doctor or a qualified health 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

Many pharmacological studies have demonstrated that extracts and isolated constituents of *Panax ginseng* display many (often interconnected) properties *in vivo* and *in vitro*. Among them effects on metabolism, immune system, nervous system and behaviour, cardiovascular system, sexual organs and skin have been investigated in animal models. Investigations of e.g. cytoprotective effects, anti-inflammatory effects, antimicrobial effects, and anti-cancer effects, including studies on the mechanism of action have been preferably conducted with isolated ginsenosides in various cell culture models. A systematic review of all of these studies will not be attempted here; a selection of studies with emphasis on studies with relevance for the clinical efficacy/plausibility of traditional use is presented.

Pharmacological data regarding herbal preparations

In many cases, especially in older studies, the ginseng preparations are not characterized sufficiently. However, in the last years several reviews were published providing information on the pharmacological properties of "ginseng" (e.g. Lee *et al.* 2005, Hofseth & Wargovich 2007, Attele *et al.* 1999, Chen *et al.* 2008, Choi 2008). In the following section pharmacological data on the well-defined herbal preparation G115 is presented.

Data obtained with a dry extract [DER 3-7:1, extraction solvent ethanol 40% V/V containing 4% ginsenosides (sum of Rb_1, Rb_2, Rc, Rd, Re, Rf, Rg_1, Rg_2) usually referred as G115], herbal preparation D, in animals:

Pannacci *et al.* (2006)

Pannacci *et al*. (2006) investigated the effects of G115 on anti-inflammatory cytokine production and toll-like receptor 4 (TLR4) RNA expression in mice during 4 weeks of swimming stress. Male 6-week-old BALB/c pathogen-free mice were assigned randomly to four groups: control (no exercise), control G115 (25 mg/kg/day p.o.), stress (swimming for 60 min daily), stress-G115 (25 mg/kg/p.o., swimming for 60 min daily). RNA from peritoneal macrophages was extracted and analysed. An aliquot of macrophages was LPS-stimulated for TNF-α and IL-1β production *in vitro*. High levels of TLR 4 expression in the control-G115 group were detected at the first and second week. In the stress-G115 group, the levels of TLR4 expression increased gradually at the second week with a peak at the third week. Levels of TLR-expression at the fourth week had returned to the basal level. Levels of TLR2 expression were not affected by treatment in all groups. A significant increase of LPS-stimulated IL-1β and TNF-α concentration was present in trained animals with a similar pattern of TLR4 expression. The authors stated that toll-like receptors are regarded to play a critical role in recognition of pathogens and in initiation of immune response and that therefore their findings provided a contribution to an understanding of how physical stress and ginseng extract might modulate the innate immune cell response. The authors concluded that G115 seemed to modulate immune response by reducing the peak of cytokine release after the first weeks of stress and stimulated the innate immune response gradually facilitating host defence and potentiating the response against bacterial or pathogenic challenge.

Wu *et al.* (2001)

Wu *et al*. (2001) investigated the preventive effects of G115 on balloon injury-induced neointima formation (restenosis) in Sprague-Dawley rats (300-400 g). Animals (n=6 per group) were pre-treated with G115 (2 mg/kg b.w. or 200 mg/kg b.w. orally) for 7 days followed by balloon injury. Furthermore an ex vivo assay of G115 on contractions of aortic strips (tissue bath: 0.18, 0.36, 0.72, 1.44, and 2.88 mg/ml). Norepinephrine-induced vasocontraction was antagonized in 21% and 44% by 1.44 mg/ml and 2.88 mg/ml of G115, respectively. Neointima-to-lumen area ratio of balloon injured rat carotid arteries was reduced 77.3% by G115 as compared to the sham-operated control.

Voces *et al.* (1999)

Voces *et al*. (1999) investigated the effects of administration of G115 on hepatic antioxidant function after exhaustive exercise. Male Wistar rats (200±50g) were assigned to treatment groups of either 3, 10, or 100 mg/kg b.w. orally for 3 months or untreated control. After the treatment period animals were subjected to exhaustive exercise on a treadmill. The results showed that the administration of G115 significantly increased the hepatic glutathione peroxidase activity and reduced glutathione levels in the liver. After exercise reduced hepatic lipid peroxidation was found in treated and untreated animals. The glutathione peroxidase and superoxide dismutase activity also significantly increased in the groups receiving G115 compared to control groups. The levels of Alanine-amino transferase and Aspartate-amino-transferase showed significantly lower levels under dosages of 10 mg and 100 mg/kg of G115 compared to control groups, indicating less damage to the liver. The study-results indicated that at hepatic level G115 increased the antioxidant capacity with a marked reduction of the oxidative stress induced by exhaustive exercise.

Van Kampen *et al.* (2003)

Van Kampen *et al*. (2003) investigated the neuroprotective actions of the ginseng extract G115 in two rodent models of Parkinson's disease. Female Sprague-Dawley rats (250-275 g) and C57B16 mice (23-26 g) received oral administration of G115 (mice: 0.25, 75, 200 or 500 mg/kg/day in drinking water; rats: 100 mg/kg/day in drinking water;) 10 days prior and 10 days following the neurotoxin infusion (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or 1-methyl-4-phenylpyridinium). G 115 treatment significantly blocked tyrosine hydroxylase-positive cell loss in the substantia nigra and reduced the appearance of locomotor dysfunction. Thus, the authors concluded that oral administration of G115 appeared to provide protection against neurotoxicity in rodent models of Parkinson's disease.

Kim *et al.* (1990)

Kim *et al*. (1990) investigated the effects of orally applied G115 on morphine analgesia, development of morphine-induced tolerance and physical dependence, hepatic glutathione levels and the effects of intraperitoneally applied G115 on the dopamine receptor supersensitivity, and the reverse tolerance to the locomotor accelerating effect of morphine in white ICR male mice (20-23 g). G115 did not influence morphine analgesia at doses of 50, 100, 200, and 400 mg/kg G115. The development of morphine-induced tolerance and physical dependence was inhibited by G115 at doses of 50, 100, 200, and 400 mg/kg of G115. Furthermore, G115 inhibited the decrease of the hepatic glutathione level induced by morphine multiple injections at orally applied doses of 50, 100, 200, and 400 mg/kg. After imp. injection of 100 mg/kg G115 inhibited the development of morphine-induced dopamine receptor supersensitivity and the reverse tolerance to the locomotor accelerating effect of morphine. The authors concluded that G115 could be developed for the treatment of morphine tolerant/dependent patients.

Samira *et al.* (1985)

Samira *et al*. (1985) studied the effect of G115 on the metabolic activity and electrocorticogram of the rabbit's brain. The elcectrocorticogram of adult rabbits of both sexes (1.5-2 kg) was recorded after i.p. administration of G115 at doses of 2.3, 4.7, and 9.3 mg/kg b.w. Furthermore, *in vitro* experiments on brain tissue incubated with a glucose containing medium and G115 in doses of 23 and 46 µg/ml were conducted. The *in vitro* experiments showed a dose-related significant increase of the glucose uptake with simultaneous significant reduction of the lactate, pyruvate, and lactate/pyruvate ratio in the presence of G115 indicating changes in the metabolic pathways and improving the energy balance of neuronal cells. Furthermore G115 was found to have a stimulant, desynchronizing action on the electrocorticogram of conscious rabbit brain. The effect started 10 minutes after i.p. injection and was maintained for more than 2 hours.

Pharmacological data regarding isolated compounds

Studies with ginsenosides in animals:

Effects on metabolism:

Author (year)	**Compound**	**Animal model**	**Outcome**
Park *et al.* (2002)	Rb_1	Male Sprague Dawley rats (200 g); 3 groups (n=5 per group): administration of 1 or 10 mg/kg b.w. Rb_1 i.p. once daily for 3 days, control group received saline injection	Contents of triglycerides and cholesterol in the liver were decreased, plasma levels of triglycerides and β-lipoprotein were unaffected
Ikehara *et al.* (1978)	Rb_1	Male Wistar rats (120-140 g) on high fat diet or on control diet for 1.5, 3.0, 4.5, or 6 weeks; administration of a single dose of 5 mg/100 g b.w. Rb_1 i.p.	Activity of HMG-CoA is repressed by a high fat diet, administration of Rb_1 reverted this effect
Yokozawa *et al.* (1985a)	Rb_2	Male Wistar rats (100-110 g) on high cholesterol diet, 3 groups (n=6 per group) administration of a single dose of 10 mg Rb_2 in saline solution i.p., administration of repeated doses, administration of saline solution in the control group	Contents of serum total cholesterol, free cholesterol, LDL, triglycerides decreased, content of HDL was increased after single dose and repeated dose administration of Rb_2
Yokozawa *et al.* (1985b)	Rb_2	Male Wistar rats (90-100 g, normal and streptozotocin induced diabetic rats), 3 groups (n=6 per group), i.p. administration of 10 mg Rb_2 in saline solution daily for 6 days in diabetic rats or saline solution in the control diabetic group	Significant decrease of blood glucose level, significant decrease in the activity of glucose-6-phosphatase, significant increase of the hepatic glycogen content and glucokinase activity in the liver in diabetic rats treated with Rb_2 compared with control diabetic rats
Yokozawa *et al.* (1984)	Rb_2	Male Wistar rats (90-100 g), 2 groups (n=6 per group), administration of a single dose of 10 mg Rb_2 in saline solution i.p. or saline solution in the control group	Time course experiments after administration of Rb_2: maximum decrease of hepatic glycogen after 8h, maximum increase of glucose-6-phosphatase, maximum increase of phosphofructokinase after 12h; no significant changes in the total lipid, triglyceride, total cholesterol, phospholipid, glucose, pyruvate, and

			lactate levels in the liver
Cho *et al.* (2006)	Re	Male Sprague Dawley rats (250-300 g), 4 groups of streptozotocin induced diabetic rats (n per group unknown) treatment with 5, 10 or 20 mg/kg b.w. of ginsenoside Re orally, treatment with 20 mg/kg b.w. of PVP-10 solution in the control group; 2 groups of nomal rats (n per group unknown) treated with either vehicle or 20 mg/kg b.w. Re	Significant reduction in blood glucose, cholesterol and triglyceride levels in diabetic rats treated with Re. Levels of glutathione and malonyldialdehyde in the eye and kidney were restored to normal values
Lee *et al.* (2007, abstract only)	Rh_2	Rats (induced insulin resistance by fructose-rich diet, streptozotocin-induced diabetic rats), treatment with single (0.1-1.0 mg/kg) and repeated doses (3 times daily 1.0 mg/kg) of ginsenoside Rh_2 i.v.	Dose dependent decrease of plasma glucose concentrations after single dose administration in insulin resistant rats; decreased value of glucose-insulin index and delayed development of insulin resistance after repeated dose administration; improved insulin sensitivity in streptozotocin-induced diabetic rats after repeated dose administration
Lai *et al.* (2006)	Rh_2	Male Wistar rats (200-250 g), Male BDF1 mice, μ-receptor knockout mice; diabetes was induced by streptozotocin-treatment; different treatment and control groups (n=7 per group): single dose of 1.0 mg/kg b.w. i.v. of Rh_2 in diabetic rats or saline solution in control groups; single dose of 1.0 mg/kg in diabetic mice (normal and knockout) or saline solution in control groups; treatment with 1.0 mg/kg b.w. i.v. three times daily in diabetic rats or saline solution in control groups	Dose dependent decrease of plasma glucose concentrations after single dose administration in diabetic rats, increase of plasma β-endorphine-like immunoreactivity was observed; inhibition of plasma glucose-lowering action of Rh_2 by opioid μ-receptor-blockers in normal mice. No influence on plasma glucose-levels in opioid μ-receptor knockout mice; increase in gene expression at mRNA and protein levels of GLUT-4 transporters was observed in diabetic rats after repeated dose treatment with Rh_2 but was absent when opioid μ-receptors were blocked
Lee WK *et al.* (2006)	Rh_2	Male Wistar rats (200-250 g), single dose administration of 0.1, 0.5, or 1.0 mg/kg b.w. i.v. Rh_2 in saline solution or saline solution in control group (n=8 per group for each group) single dose administration of 1.0 m/kg b.w. i.v.	Dose dependent decrease of plasma glucose levels and dose dependent increase of plasma insulin levels and C-peptide levels was observed. These effects were reversed by atropine but were not affected by

		Rh_2 in saline solution in presence of different concentrations of atropine, 4-diphenylacetoxy-N-methylpiperidine methiodide (4-DAMP), pentolinium, hexamethonium, hemicholinium-3, and vesamicol	the ganglionic nicotinic antagonists pentolinium and hexamethonium. ACh-uptake inhibitors (hemicholinium) or Ach-transport inhibitors (vesamicol), and the M_3 receptor antagonist 4-DAMP abolished the actions of Rh_2
Yoon *et al.* (2007)	Compound K	ICR mice: single doses of 12.5 or 25.0 mg of compound K orally 30 min prior to an OGTT (1.5 g/kg b.w.); C57BL/KsJ db/db mice, 4 groups: diabetic control group, 10 mg/kg b.w. compound K, 150 mg/kg metformin, 10 mg/kg compound K + 150 mg/kg metformin ***Assessor's comment:*** for the experiments in C57BL/KsJ db/db mice the route of administration of the test compounds is not clearly stated.	OGTT: CK-treated groups had a significantly lower increase in blood glucose levels but significantly higher plasma-insulin levels Experiments in C57BL/KsJ db/db mice: all treatment groups showed significantly decreased plasma glucose levels compared to the control group with the CK+metformin treatment group being the most effective
Liu Z *et al.* (2009)	Malonyl-ginsenosides	Male Kunming strain mice (20-22 g): diabetes was induced by streptozotocin; 9 groups (n=10 per group, control groups diabetic/non-diabetic, administration of saline, 30, 60, 120 mg/kg of malonyl-ginsenosides, 120 mg/kg total saponins, 120 mg/kg panaxadiol , 4.5 mg/kg malonic acid, 120 mg/kg panaxadiol mixed with malonic acid) treated i.v. for four consecutive days	At a dose of 120 mg/kg b.w i.v. of malonyl-ginsenosides reduced the fasting blood glucose level of diabetic mice and improved glucose tolerance. Panaxadiol, malonic acid and a mixture of both compounds showed no effect

Effects on the cardiovascular system:

Author (Year)	**Compound**	**Animal model**	**Outcome**
Wu *et al.* (2011)	Rb_1	Male Sprague-Dawley rats (250-300 g), streptozotocin induced diabetes; influence of Rb_1 on myocardial ischemia and reperfusion injury was investigated; 7 groups (n=4-12 per group), Rb_1 was administered (40 mg/kg) i.v. prior to induction of myocardial ischemia and	Rb_1 reduced infarct size, cardiomyocyte apoptosis and caspase-3 activity compared to the untreated animals; effects of Rb_1 were blocked by wortmannin (specific PI3K inhibitor)

		reperfusion (30 min of coronary occlusion followed by 120 min reperfusion); infarct size, caspase-3 activity, and myocardial apoptosis were examined	
Xu *et al.* (2011, abstract only)	Rb_1	Rats, 4 groups (control, hyperhomocysteine, Rb_1 treatment, hyperhomocysteine+Rb_1); influence on homocysteine-induced endothelial dysfunction and ghrelin expression was observed by the aortic ring assay and an enzyme-linked immunosorbent assay; *in vitro* experiments were conducted in HUVEC cells to investigate the mechanism of action	Plasma ghrelin levels in the Rb_1 treated hyperhomocysteine group were significantly increased in comparison to control and untreated hyperhomocysteine group; Pathologic changes of the arterial walls in the hyperhomocysteine group were repaired by the treatment with Rb_1 via increased plasma levels of ghrelin; endothelium dependent vasodilatation function was improved by high ghrelin levels induced by Rb_1; Rb_1 also upregulates the NO signaling pathway
Chai *et al.* (2009)	Rb_1	C57BL/6J mice (12 weeks old), effects of Rb_1 on intimal hyperplasia in a guidewire injury animal model; 4 groups: control (saline), treatment with homocysteine, treatment with Rb_1, treatment with homocysteine + Rb_1 (0.35 mM via an osmotic pump) for 4 weeks; intimal-medium thickness ratios (common carotid artery, injured/normal) were calculated and local macrophage distribution was studied after the animals had been sacrificed	Rb_1 treatment led to intimal-medium thickness ratios comparable to saline group whereas treatment with homocysteine showed a significant increase; homcysteine+Rb_1 treatment showed significant improvement in the intimal-medium thickness ratios compared to homocysteine group; furthermore, Rb_1 attenuated the homocysteine induced increase of macrophage content in the injured common carotid artery
Wang *et al.* (2008)	Rb_1	Male adult Sprague-Dawley rats (260-320 g) in a myocardial ischemia and reperfusion injury model were treated with Rb_1 (40 mg/kg i.v.) 10 min prior to ischemia/reperfusion; infarct size, plasma creatin kinase, creatin kinase isoenzyme, lactate dehydrogenase and troponin T levels were measured; furthermore, Akt phosphorylation was assessed	Rb_1 preconditioning reduced infarct size compared with that in the untreated ischemia/reperfusion group; also creatin kinase, creatin kinase isoenzyme, lactate dehydrogenase and troponin T levels were markedly reduced; Akt phosphorylation expression increased after ginsenoside Rb_1 preconditioning; Rb_1 effects were inhibited by wortmannin (specific PI3K inhibitor)

Jiang *et al.* (2007)	Rb_1	Male Sprague-Dawley rats (214±13 g) with cardiac hypertrophy induced by monocrotaline; investigation of preventive and curative effects of Rb_1 on right ventricular hypertrophy; Rb_1 (10 and 40 mg/kg) was administered i.p. from day 1-14 (preventive) or day 15-28 (curative); heart weights, histological observation and expressions of mRNA and proteins of calcineurin, $NFAT_3$, and $GATA_4$ were chosen as parameters	In both groups, prevention and therapy, Rb_1 significantly decreased hypertrophic reactions, expression of arterial natriuretic peptide mRNA, calcineurin, $NFAT_3$, and $GATA_4$ in cardiocytes
Shi *et al.* (2011)	Rb_3	Male Sprague-Dawley rats (230-260 g); 5 groups (control, ischemia reperfusion group vehicle, Rb_3 group treated with 5, 10, 20 mg/kg Rb_3 orally); treatment with Rb_3 was conducted for 3 days prior to myocardial ischemia-reperfusion (30 min ischemia followed by 24 h reperfusion); myocardial infarct size, levels of creatin kinase isoenzyme, and lactate dehydrogenase, endothelin and angiotensin II in serum were measured; furthermore a histopathological investigation and assays of malonyldialdehyde and superoxide dismutase activity were performed	Rb_3 treatment resulted in a reduction in myocardial infarct size; changes of creatine kinase activity and lactate dehydrogenase activity were significantly attenuated by Rb_3; the increase of malonyldialdehyde content and the decrease of superoxide dismutase activity in left ventricle were alleviated by Rb_3; plasma endothelin and angiotensin II levels were decreased, and histopathological examination confirmed the cardioprotective activity of Rb_3
Li J *et al.* (2011)	Rd	apoE knockout mice were used for the investigation of the effect of Rd on atherosclerosis; animals were fed with a high-fat diet and divided into 4 groups (n=10 per group): preventive treatment with 20 mg/kg/day i.p. for 12 weeks, curative treatment with 20 mg/kg/day i.p. for 5 weeks after 7 weeks of high- fat diet, PEG vehicle treatment group for 12 weeks (control), saline treatment group for 12 weeks (control); measurement of atherosclerotic plaque area, oxidized LDL uptake, thapsiargin and 1-oleoyl-2-acetyl-glycerol induced Ca^{2+}	Rd (20mg/kg/day i.p. preventive and therapeutic) reduced significantly the atherosclerotic plaque areas, oxidized LDL uptake and thapsiargin and 1-oleoyl-2-acetyl-glycerol induced Ca^{2+} influx in macrophages; increased levels of lipoproteins and blood lipids were not changed by Rd

		influx in macrophages were used as parameters	
Liu *et al.* (2002)	Re	Male and female Wistar rats (200-250 g) were used in an ischemia (30 min)/reperfusion (6 h) model to investigate the effects of Re on myocardial ischemia/reperfusion; i.v. injection of 20 mg/kg of Re 10 min before ischemia, control group received saline injection; morphology of cardiomyocyte apoptosis, mRNA and protein expression of Bcl-2 and Bax were investigated	Re significantly inhibited cardiomyocyte apoptosis and inhibited the expression of the pro-apoptotic Bax gene but did not influence the expression of Bcl/2, thus resulting in an increase of the ratio of Bcl-2/Bax
Deng *et al.* (2010)	Rg_1	Male Sprague-Dawley rats (200±20 g) were used to investigate the influence of Rg_1 on left ventricular hypertrophy induced by abdominal aorta coarctation and its mechanism of action; treatment group received 15 mg/kg/day i.p. alone or in combination with orally applied L-arginine or N^G-nitro-L-arginine-methyl ester (NOS inhibitor) from day 1 after surgery for 21 consecutive days; weight of the left ventricle, mRNA expression of atrial natriuretic peptide and histopathological investigations were chosen as parameters for determination of cardiac hypertrophy	Rg_1 and L-arginine significantly reduced the elevated left ventricular hypertrophic parameters and ameliorated the histopathology of left ventricular myocardium and diastolic function; the beneficial effects of Rg_1 were inhibited by N^G-nitro-L-arginine-methyl ester
Deng *et al.* (2009)	Rg_1	Male Sprague-Dawley rats (8-12 weeks old, 200±20 g) were used to investigate the influence of Rg_1 on left ventricular hypertrophy induced by abdominal aorta coarctation and its mechanism of action; 5 groups: operated and sham-operated control groups received distilled water, treatment group received 3.75, 7.5, and 15 mg/kg/day i.p. for 21 consecutive days after surgery; measured parameters were elevated weight of the left ventricle, expression of atrial natriuretic peptide, expressions of calcineurin, kinase-1, and mitogin-	Rg_1 significantly ameliorated left ventricular hypertrophy in a dose-dependent manner showing best results at 15 mg/kg/day; the expression of MAP kinase phosphatase 1 was increased by Rg_1; mRNA expression of atrial natriuretic peptide was reduced significantly, expression of calcineurin and kinase 1 was decreased significantly

		activated protein kinase phosphatase 1	
Chang *et al.* (2006)	Rg_1	New Zealand White rabbits (2.5-3.0 kg) were used to investigate the angiogenic effects of Rg_1 in a model to reduce postsurgical pericardial adhesions; cellular bovine pericardium patch, acellular bovine pericardium patch with and without loading of Rg_1 were implanted; for loading of Rg_1 the sterilized acellular patch was submerged in an aqueous solution of 10 mg/ml of Rg_1 for 36 h; the implanted samples were retrieved at 1 and 3 months after surgery and inspected macro- and microscopically	The acellular patches significantly reduced postsurgical pericardial adhesions; in the presence of Rg_1 a faster remesothelialization was observed on each side of the patch; there was still a filmy adhesion to the epicardium obserced in 3 of the 5 studied animals at 3 months after surgery
Matsuda *et al.* (1986)	Ro	Male Wistar-King strain rats (150-200 g) were used to investigate the antithrombic activity of Ro in an experimental model of disseminated intravascular coagulation induced by infusion of endotoxin or thrombin; animals received 10 or 50 mg/kg orally 1 h prior to the injection of endotoxin; blood samples were taken 4 h after injection for determination of fibrinogen levels, fibrin degradation product, prothrombin time and count of blood platelets	Ro (50 mg/kg p.o.) showed o promotive effect on the activation of the fibrinolytic system; reduction of blood platelet count and fibrinogen level by endotoxin was attenuated by Ro; shortening of the prothrombin time was observed in Ro treated animals
Han *et al.* (2011, abstract only)	20(S)-protopanaxatriol	Male Wistar rats were used to investigate the effects of 20(S)-protopanaxatriol in a model of myocardial injury induced by isoproterenol; animals received 20(S)-protopanaxatriol orally for 7 days, four days after treatment isoproterenol was injected s.c. for 3 consecutive days; malondialdehyde levels, superoxide dismutase activity, glutathione peroxidase and total antioxidant capacity were investigated	20(S)-protopanaxatriol inhibited the elevation of malondialdehyde content, reduction of superoxide dismutase activity, glutathione peroxidase and total antioxidant capacity in heart tissue; pathohistological changes induced by isoproterenol were ameliorated

Effects on the nervous system / behaviour:

Author (Year)	Compound	Animal model	Outcome
Yamada *et al.* (2011)	Rb_1, Rg_1, Rg_3, Ro, compound K, protopanaxadiol	ICR albino female mice, menopausal depressive-like state; non-treated intact, ovariectomized at 9 weeks of age, sham-operated mice, and vehicle as control-groups (n=8 per group); treatment groups of ovariectomized mice (n=8 per group) received white ginseng powder (100, 200, 400 mg/kg b.w. p.o daily), red ginseng powder (100, 200, 400 mg/kg b.w. p.o daily), ginseng non-saponin-fraction (50, 100, 200 mg/kg b.w. p.o daily), ginseng saponin-fraction (25, 50, 100 mg/kg b.w. p.o. daily), pure ginsenosides (Rb_1, Rg_1, Ro, Rg_3, protopanaxadiol: 2.5, 5, 10 mg/kg b.w. i.p. daily; compound K: 1.25, 2.5, 5 mg/kg b.w. i.p); coadministration of ritanserin (5-HT_{2A}-receptor antagonist) with Rb_1	Forced swimming test and investigation of the general motor activity were conducted; the highest doses of red ginseng, white ginseng and ginseng saponin-fraction significantly prevented the prolongation of immobility; ginsenoside Rb_1, Rg_3, and compound K dose-dependently prevented the prolongation of immobility time induced by ovariectomy, which is associated with an anti-depressant activity. Co-administration of ritanserin antagonized the effect of ginsenoside Rb_1; metabolites of Rb_1 (Rg_3, compound K) increased the uterine weight of the ovariectomized mice
Hao *et al.* (2011)	Rb_1	Female ovariectomized Swiss-Hauschka mice (18-22 g) with tryptophan-free diet; 7 groups (n=8 per group): control group (tryptophan), model group (tryptophan-free), Rb_1-group (tryptophan-free, i.v.-injection of Rb_1, estradiol-group (tryptophan-free, i.v.-injection of estradiol), clomiphene+estradiol-group, clomiphene-group, clomiphene+ginsenoside-group; doses: Rb_1 20 mg/kg, estradiol 0.2 mg/kg, clomiphene 8 mg/kg; treatment was acute (single dose), chronic (twice daily for 7 days), preventive (twice daily for 14 days prior to tryptophan or tryptophan-free diet); brain samples were collected 2 h after treatment with single dose, doses on day 7 and day 14 and investigated for neurotransmitter	Administration of Rb_1 increased the neuronal 5-HT concentration, elevated the tryptophan hydroxylase activity and decreased the MAO activity; object recognition was improved, immobility time in the forced swimming test was decreased; pretreatment with clomiphene blocked the Rb_1 effects

		concentration (e.g. tryptophan, kynurenine, 5-HT, dopamine, norepinephrine) and enzyme activity (tryptophan hydroxylase, MAO, aromatic amino acid decarboxylase); Object recognition memory, forced swimming test and locomotor activity were tested 1h after treatment with single dose	
Liu *et al.* (2011)	Rb_1	Male Sprague-Dawley rats (270-300 g), 12 weeks old, control and Rb_1-group; each group was subdivided into three subgroups: behavioural test (Morris water maze), cell survival/cell prolongation in the hippocampus: BrdU incorporation; administration of 2 mg/kg b.w. of Rb_1 in drinking water for 30 days	Rb_1 improved spatial cognitive performance in Morris water maze; Rb_1 significantly increased the cell survival in dentate gyrus and hippocampal subregion CA3 but had no significant influence on cell proliferation in the hippocampal subregions
Li Y *et al.* (2011, abstract only)	Rb_1	Male Sprague-Dawley rats (250-300 g), three-groups: Sham-group (n=10), vehicle group (n=12, subarachnoid hemorrhage+no treatment), treatment group (n=11, subarachnoid hemorrhage+ 20 mg/kg Rb_1 i.v.); post-operative assessment included neurobehavioural testing using the spontaneous activity scoring system, brain water content, and histological examination of the basilar artery	Rb_1 reduced significantly the brain edema and improved neurobehavioral functioning, histological examination revealed a significant reduction in basilar artery vasospasm and lumen thickness
Zhang *et al.* (1998)	Rb_1	SH-BP rats (250-320 g, 12-13 weeks old), left middle cerebral artery (MCA) was coagulated and cut; different groups (n=8 per group): MCA-occluded animals infused with saline, sham-operated animals infused with saline, and treatment groups; Rb_1 was administered for 4 weeks at doses of 0.006 to 6.0 µg/day by intracerebroventricular infusion into the left lateral ventricle either 2 hours before or immediately after the MCA occlusion; Morris water-maze test, Inclined screen-test and Rotating rod-test were performed for	Rb_1 significantly decreased escape latency on repeated trials of the Morris water maze test throughout the first to the fourth trial days at 2 and 4 weeks after MCA occlusion; The ratio of the infarcted area to the left hemispheric area in the groups treated with 0.6 µg/day Rb_1 was significantly smaller than in the control groups, significant differences were observed in the neuron numbers in the ventroposterior thalamic nucleus and in the left-to-right ratio of the thalamic area between treatment

		behavioral investigations; brains were examined morphologically; furthermore, antioxidative effects of Rb_1 were tested in a cell-culture model (neurons of 17-day-old rat embryos stressed with $FeSO_4$): survival rate of the cells was determined	and control-groups; Rb_1 facilitated neurite extension and rescued cortical neurons from lethal damage caused by the free radical-promoting agent $FeSO_4$ *in vitro*
Wang & Zhang (2003)	Rb_1	Male SD rats, anaesthetized with urethane carbamate; The effect of Rb_1 (10, 100 nmol/L, icv) on the population spike (PS) amplitude and the maintenance phase of long-term potentiation (LTP) induced by high frequency stimulation in the dentate gyrus was investigated to determine the influence of Rb_1 on synaptic transmission	Rb_1 decreased the PS amplitude and inhibited the efficacy of synaptic transmission in a dose-dependent manner. Furthermore Rb_1 exhibited a positive effect on the maintenance phases of LTP and increased LTP expression in a dose-dependent manner in anaesthetized rats
Churchill *et al.* (2002)	Rb_1	Male Cornish Rock cockerels, 5 days old; 4 groups (n=20 per group): 0, 0.25, 2.5, 5.0 mg/kg b.w. i.p of Rb_1; visual discrimination learning was assessed on an apparatus suitable to evaluate the effects of nootropics in chicks (food pellets vs. pebbles); total number of errors (pecks directed at rocks), first response latency, and the amount of time required to complete the task were recorded; in a second experiment (same posology, n=16 per group) separation distress was evaluated (anxiety setting using chambers with or without mirrors for separated animals)	Acquisition of a visual discrimination task was unaffected by drug treatment, but the number of errors was significantly reduced in the 0.25 mg/kg group during retention trials completed 24 and 72 hours after injection. Rb_1 had no effect on response rates or body weight. In the second experiment Rb_1 produced a dose dependent change in separation distress suggesting that nootropic effects may be related to changes in anxiety
Wang & Lee (2000)	Rb_1, Rg_1	Male Sprague-Dawley rats (3-6 months old, average b.w. of 411.8 g and 26-28 months old, average b.w. of 432.5 g); effects of ginsenoside mixtures (5, 10, 20 mg/kg with and without Rb_1 and Rg_1), Rb_1 (2.5, and 5.0 mg/kg) and Rg_1 (2.5, and 5.0 mg/kg) after i.p. injection on cold tolerance of young and elderly rats were examined by measuring heat production, oxygen consumption and carbon dioxide production	Pretreating the animals with Rb_1 but not Rg_1 increased thermogenesis as well as cold tolerance in young rats and elderly rats

Lim *et al.* (1997)	Rb_1	Male Mongolian gerbils (70-80 g, 12 weeks of age); animals (n=8 per group) were subjected to 3.5 or 3 min of forebrain ischemia, immediately after TIA 2 µl of isotonic saline containing 2.5 or 25 ng Rb_1 or the same volume of saline alone was injected into the left lateral ventricle; an osmotic minipump was implanted subcutaneously releasing 60 or 600 ng/day for 7 days into the lateral ventricle; other groups of animals received 10 or 20 mg/kg i.p. of Rb_1 once daily for 7 days before or after 3.5 min of forebrain ischemia; after 7 days the animals were examined with a step-down passive avoidance apparatus; subsequently animals were sacrificed for a histopathological examination; during the experiments hippocampal blood flow and temperature were monitored; antioxidative properties were studied in a cell culture model using hippocampal neurons of 17 day old rat embryos treated with $FeSO_4$	The intracerebroventricular infusion of ginsenoside Rb_1 after 3.5 or 3 min forebrain ischemia precluded significantly the ischemia-induced shortening of response latency in a step-down passive avoidance task and rescued a significant number of hippocampal neurons from lethal ischemic damage. Hippocampal blood flow or temperature was not affected; furthermore, Rb_1 rescued hippocampal neurons from lethal damage caused by the hydroxyl radical-promoting agent $FeSO_4$ *in vitro*
Abe *et al.* (1994, abstract only)	Rb_1, Malonyl-ginsenoside Rb_1	Anaesthetized rats, icv application of 0.5-50 nmol Rb_1 and Rb_1-m	Rb_1 did not affect the basal synaptic responses evoked by low-frequency test stimulation, but significantly attenuated the magnitude of long-term potentiation (LTP) induced by strong tetanus in the dentate gyrus. m-Rb_1 did not affect the LTP induced by the strong tetanus but facilitated the generation of LTP by the weak tetanus
Etou *et al.* (1988, abstract only)	Rb_1	Rats received infusion of 0.05, 0.10, and 0.20 µmol Rb_1 into the third cerebroventricle; furthermore effects of injection of 0.01 µmol of Rb_1 into the hypothalamic ventromedial nucleus and into the hypothalamic area	Rb_1 infusion potently decreased food intake dose-dependently; drinking episodes decreased concomitantly with feeding suppression only at the highest dose; plasma glucose was increased, insulin

		were investigated	levels were unaffected. Microinjection into the hypothalamic ventromedial nucleus decreased food intake, injection into the lateral hypothalamic area did not
Cui *et al.* (2012)	Rb_3	Male NIH mice (18-20 g) for behavioral experiments, unweaned Sprague-Dawley rats (14-18 days old) were used in the electrophysiological experiments; Doses of 30, 75, and 150 mg/kg b.w. were administered intragastrically; fluoxetine 10 mg/kg b.w. served as positive control; open field test, forced swim test, tail suspension test, and learned helplessness procedure were applied as a behavioral despair model; Locomotor activity test, novelty-suppressed feeding test, and sucrose preference test served for the assessment of the behavior in chronic mild stress conditions; furthermore the levels of monoamine neurotransmitters, frequency and amplitude of action potentials were investigated in different brain regions	Rb_3 showed dose-related significant anti-immobility effects in mice in the forced swim and tail suspension test and reduced the number of escape failures in the learned helplessness procedure. Furthermore, the decrease in locomotor activity, novelty-suppressed feeding, and sucrose preference induced in the chronic mild stress model was reversed by Rb_3 administration; the action potential transmission in neurons within the somato-sensory cortex was excited by Rb_3 perfusion and Rb_3 showed an influence on the neurotransmitter-regulation
Li L *et al.* (2011)	Rd	Adult male Sprague-Dawley rats (200-250 g) in an AD model induced by the microinjection of 200 ng okadaic acid (OA) into cerebral ventricle; 5 groups of animals (n=14 per group): normal group, control group, OA 1 and OA 2 group(animals were sacrificed 1 or 2 weeks after the injection of OA), treatment group (pretreatment with 10 mg/kg Rd 7 days prior to injection of OA, animals were sacrificed 2 weeks later); brain tissue was investigated histologically and assayed for protein phosphatase 2A activity; furthermore, the neuroprotective effects of Rd (2.5 or 5.0 µmol/L for 12 h) on cultured cortical neurons were investigated	Pretreatment with Rd reduced OA-induced neurotoxicity and tau hyperphosphorylation by enhancing the activity of protein phosphatase 2A

		Assessor's comment: The route of administration in the animal model is not described	
Ye *et al.* (2011a)	Rd	Male C57BL/6 mice (16-18 months old) with middle cerebral artery occlusion (MCAO); 0.1-200 mg/kg i.p. of Rd 30 min before MCAO onset in a dose response-study, 50 mg/kg i.p. starting at 2 h, 4 h, 6 h or 10 h after the onset of MCAO in a therapeutic window study; control-group received vehicle; behavioral tests: postural reflex test, forelimb placing test; furthermore immunohistochemistry tests, biochemistry tests, enzyme assays ***Assessor's comment:*** Similar studies as described above were conducted in Sprague-Dawley rats (Ye *et al.* (2011b, c, d) with similar results using slightly different behavioral tests and focusing on the effects of Rd on mitochondria and the mechanism of action	Rd at doses of 10-50 mg/kg b.w. significantly reduced both cortical and striatal infarct volume; furthermore improvement in neurological function, even when administered up to 4 h after recirculation; Rd partly enhanced endogenous antioxidant activities, protected mitochondria and significantly suppressed the accumulation of DNA, protein, and lipid peroxidation products
Yokozawa *et al.* (2004, abstract only)	Rd	Senescence-accelerated mice (10 months old); administration of 1 or 5 mg/kg b.w. of Rd once daily for 30 days; parameters of the antioxidative defence system were measured ***Assessor's comment:*** The route of administration is not mentioned in the abstract, the full article was not available	Administration of Rd resulted in the elevation of the glutathione/glutathione disulfide ratio, activity of glutathione peroxidase and glutathione reductase were increased; Rd did not affect the superoxide dismutase and catalase activity but inhibited lipid peroxidation
Lee JK *et al.* (2003)	Rb_1, Rb_2, Rc, Rd, Re, Rf, Rg_1, Rg_2, Rg_3	Male ICR-mice (26-30 g); neurotoxicity was induced by intracerebroventricular microinjection of kainic acid; animals were pretreated with single ginsenosides (i.c.v. injection 10 min prior to kainic acid, doses of 50 µg except Rd: 1-50 µg), survival time of the animals was	Administration of Rd i.c.v. attenuated the KA-induced lethal toxicity

		examined	
Nemmani & Ramarao (2003)	Rf	Swiss male mice (20-26 g) with U50-induced analgesia received low doses of Rf i.p (10^{-14}, 10^{-12}, 10^{-10} mg/kg); in tolerance studies Rf was administered once daily; flumazenil (0.1 mg/kg) and picrotoxin (1 mg/kg) were co-administered to get insight into the mechanism of action of Rf	Rf potentiated the U50 induced analgesia on co-treatment dose-dependently and inhibited the tolerance to U50-induced analgesia; The inhibition of tolerance was not altered by the $GABA_A$-gated chloride channel blocker picrotoxin or by the benzodiazepine receptor antagonist flumazenil
Qi *et al.* (2009)	Rg_1	Male Sprague-Dawley rats (180-200 g); chronic treatment with morphine (10 mg/kg s.c. twice daily); control group received saline injection; Rg_1 (30 mg/kg) was administered i.p. once daily 2 h after the second morphine injection; The influence of Rg_1 on morphine induced impairment in the Morris water maze test was investigated	Rg_1 decreased the morphine induced escape latency and increased the time spent in platform quadrant and entering frequency. Furthermore Rg_1 restored the long-term potentiation impaired by morpine in both, freely moving and anaesthetized rats
Kang *et al.* (1995)	Rg_1	Mature male Wistar King A rats (280-330 g); effects of Rg_1 on IL-1β induced suppression of food and water intake and body temperature were investigated; animals were divided into 4 groups: control with and without IL-1β treatment, IL-1β treated animals receiving Rg_1 or vehicle; 4.0 mM solution of Rg_1 in phosphate buffered saline was infused continuously via an osmotic minipump into the third cerebroventricle	The suppressive effect of IL-1β on water intake was converted to an increase by Rg_1, the elevation of rectal temperature induced by IL-1β was attenuated by Rg_1; the feeding suppression was unaffected
Fujimoto *et al.* (1989)	Rg_1	Mature male Wistar King A rats (270-320 g); effects of Rg_1 on modulation of ingestive behavior were investigated; animals received acute infusions of 10 µl of 1.0, 2.0, 4.0, or 8.0 mM of Rg_1 in phosphate buffered saline solution into the third cerebroventricle for 10 min. Another group received continuous infusion of 4.0 mM Rg_1 in phosphate buffered saline via an osmotic	No direct effect was observed on food intake after acute infusion, continuous osmotic infusion of 4.0mM Rg_1 into the third cerebroventricle prevented feeding suppression and attenuated anorexia. Rg1 increased water intake was increased and decreased ambulation that was produced by elevation of environmental temperature; rats maintained body weight and rectal

		minipump	temperature unchanged
Zhang G *et al.* (2008)	Rg_2	Male Sprague-Dawley rats (250-300 g), divided into seven groups (n=8 per group): control, sham-operated, vascular dementia model (VD), Rg_2 (2.5, 5.0, and 10.0 mg/kg i.v.)-treated VD model and nimodipine (50 µg/kg i.v.)-treated VD model; VD was induced by occlusion of the middle cerebral artery for 1 h, circulation was restored for 48 h; effects of Rg_2 on memory impairment were investigated in the Y-maze test	Neurological responses and memory ability improved significantly in the groups treated with Rg_2 or nimodipine compared with the VD-model; Immunohistochemistry investigations indicated an influence of Rg_2 on the expression of apoptotic related proteins
Ma & Yu (1993)	Rg_2	Male Wistar rats; effects of Rg_2 on acquisition, retention, and retrieval were examined in a two-way active avoidance method; 20 mg/kg Rg_2 was administered i.p. repeatedly	Administration of Rg_2 led to a significant improvement of recognitional deficits in day 3 learning acquisition, in 48 h memory acquisition, in 24 h memory retention, and in 48 h memory retrieval
Yang YH *et al.* (2009)	Rb_1, Rg_3, Rh_2	Male ICR mice (28-30 g) in a scopolamine induced learning deficit model; ginsenosides were administered p.o (10, 20, 40 mg/kg); positive control: tacrine 10 mg/kg p.o.; influence of ginsenosides on learning and memory was investigated in passive avoidance test, Y-maze test and Morris water maze test	Among the tested ginsenosides Rh_2 most potently reversed memory impairment caused by scopolamine and significantly shortened the escape latencies in the Morris water maze test, increased the swimming time within the platform quadrant
Park *et al.* (2004)	Rh_2	Male Sprague-Dawley rats (270-280 g) with induced transient cerebral ischemia (occlusion of the middle cerebral artery); Rh_2 (100 mg/kg) was administered orally immediately prior to reperfusion (n=5 per group); control group (n=10) received vehicle orally	Orally administered Rh_2 significantly reduced the infarct area caused by MCA occlusion.
Xu *et al.* (2010)	20(S)-protopanaxadiol	Male Swiss mice (18-22 g), male Sprague-Dawley rats (200-250 g); tail suspension test , forced swimming test, passive avoidance test, sweet-water consumption test and other tests were performed to investigate the antidepressant effects of 20(S)-protopanaxadiol; doses	20(S)-Protopanaxadiol showed anti-depressant effects in all tests as potent as fluoxetine; brain oxidative stress was reduced significantly and serum corticosterone levels were down-regulated; the monoamine reuptake activity was rather weak

		of 3.75, 7.5, and 15 mg/kg were applied orally in tail suspension tests and forced swimming tests; doses of 3.3, 6.6, and 13.3 mg/kg were applied orally in the passive avoidance tests and sweet water consumption tests; fluoxetine at 18 and 16 mg/kg orally served as positive control	

In vitro studies with isolated ginsenosides:

Rausch *et al.* (2006)

Rausch *et al*. (2006) reviewed the neuroprotective effects of ginsenosides. Ginsenosides Rb_1 and Rg_3 protected cultured rat cortical cells from glutamate-induced neurodegeneration (Kim *et al.* 1998). In a study by Radad *et al.* (2004) primary dopaminergic neurons from embryonic mouse mesencephala were exposed to a neurotoxic glutamate concentration. Pre-treating and post-treating with ginsenosides Rb_1 and Rg_1 to glutamate exposure significantly increased the numbers and lengths of neurites of surviving dopaminergic cells. Thus ginsenosides Rb_1 and Rg_1 appeared to exert partial neurotrophic and neuroprotective functions against glutamate in cell culture. Ginsenosides promoted cell proliferation and enhanced the survival rate of new-born cells. Neuroprotective effects in ischemia models could reflect the energetic sparting by preserving ATP stores. A rise of free radicals due to environmental toxins and mitochondrial dysfunction could be counteracted by different ginsenosides given their different potencies as antioxidants and free radical scavengers. *In vitro* the orders of antioxidative ability has been established by Liu *et al*. (2003) as follows: $Rc>Rb_1$ and $Re>Rd>R1>Rg_1>Rb_3>Rh_1$. Most effects of ginsenosides are related to their NMDA-receptor actions, counteracting excitotoxicity by glutamate. In particular ginsenoside Rg_3 inhibits both NMDA and non-NMDA glutamate receptors (Kim *et al.* 2002, Kim *et al.* 2004). These actions result in a reduction of Ca^{2+} over-influx into neurons and thus protect cells from neurodegenerative processes evoked by Ca^{2+} overload (Liao *et al.* 2002). Anti-inflammatory activity of ginsenosides Rb_1 and its metabolite compound K on lipopolysaccharide stimulated murine macrophages were studied. Compound K potently inhibited the production of NO and prostaglandin E2 reduced the expression levels of the inducible NO synthase and COX-2 proteins, and prevented the activation of NF-kB (Park *et al.* 2005). Antiapoptotic effects have been tested for ginsenosides in PC12 cells and Rg_1 had a protective effect against MPTP-induced apoptosis in the mouse substantia nigra. This anti-apoptotic effect was attributed to enhanced expression of Bcl-2 and Bcl-xl, reduced expression of bax and nitric oxide synthase, and inhibited activation of caspase-3 (Chen *et al.* 2002, Kim EH *et al.* 2003).

Nah *et al.* (2007)

Nah *et al*. (2007) reviewed the effects of ginsenosides on the central nervous system. In rat sensory neurons ginsenosides Rb_1, Rc, Re, Rf, Rg_1, Rg_3, and Rh_2 (100 µM) appeared to be Ca^{2+}channel regulators. In particular Rh_2 and compound K inhibit different Ca^{2+} channel subtypes selectively. Furthermore, ginsenosides (100 µM) also attenuated the stimulated membrane capacitance increase in rat chromaffin cells. These findings suggested that ginsenosides might be closely involved in the regulation of neurotransmitter release. Investigations in rabbit coronary artery smooth muscle cells showed that total saponins (50-500 µg/ml) and ginsenoside Rg_3 (100 µg/ml) activate Ca^{2+}-activated and ATP-sensitive K^+-channels. Furthermore Ca^{2+}-activated K^+-channels were activated and NO secretion was increased in cultured endothelial cells by ginsenosides. G-protein-coupled inwardly rectifying K^+- channels expressed in *Xenopus* oocytes were activated by Rb_1, Rg_1, and Rf. Other investigations showed that ginsenoside Rg_3 inhibited voltage dependent K^+-channels expressed in *Xenopus* oocytes. Voltage-dependent brain-specific Na^+-channels expressed in A201 cell lines and Xenopus oocytes were inhibited by ginsenosides (3 mg/ml of an extract and 150 µg/ml of Rg_3). Rg_3 has been reported to be effective also at a concentration of 100 µg/ml. Among ligand-gated ion channels ginsenosides showed effects on NMDA gated ion channels (most effective Rg_3, Rb_1, Rg_1 in rat cortical cultures, cultured hippocampal neurons, astrocytes, and the dentate gyrus), nicotinic acethylcholine ligand-gated ion channels (panaxatriol ginsenosides more effective than panaxadiol ginsenosides in inhibiting Ach-induced inward currents), serotonin-gated ion channels and $5\text{-}HT_3$ receptors (Rg_2, compound K, ginseng metabolite M4, Rg_3). Furthermore investigations on the stereospecificity of ginsenosides at 100 µM showed that 20(S)-ginsenoside Rg_3 but not 20(R)-

ginsenoside Rg_3 inhibited voltage dependent Ca^{2+}, K^+, and Na^+-channel activities. Similar effects have been observed on 5-HT_3 and α3β4 nicotinic acetylcholine receptor channel activities.

Attele *et al.* (1999)

Attele *et al*. (1999) reviewed antineoplastic and immunomodulatory effects of ginseng and ginsenosides among other pharmacological actions. Ginsenoside Rh_2 inhibited growth and stimulated melanogenesis and arrested cell cycle progression at the G_1 stage in B16-BL6 melanoma cells associated with a suppression of cyclin-dependent-kinase-2 activity. Furthermore the ginsenoside metabolite M1 inhibited the proliferation of B16-BL6 mouse melanoma cells and in higher concentrations induced cell death within 24h by regulating apopotosis-related proteins. Other studies demonstrated that Rh_2 and Rh_3 induced differentiation of promyelocytic leukemia HL-60 cells into granulocytes. Rg_3 significantly inhibited the adhesion and invasion of B16-BL6 cells into reconstituted basement membranes and inhibited pulmonary metastasis. Ginsenosides have been shown to influence the humoral and cellular immune system, especially natural killer cells and the authors concluded that these activities might also contribute to anti-cancer effects of ginseng.

Studies on polysaccharides (panaxans):

So far very few studies have been conducted on panaxans but these investigations in animal models show that besides the ginsenosides also polysaccharides may contribute to the effects of *Panax ginseng.*

Several panaxans showed hypoglycaemic activity in normal and diabetic mice (Konno *et al.* 1984, Konno *et al.* 1985, Oshima *et al.* 1985, Ng & Yeung 1985, only abstract available). Recently, antidepressant and anti-fatigue effects of a polysaccharide fraction (100 and 200 mg/kg) extracted from ginseng roots have been detected in a mouse model (Wang *et al.* 2010a, Wang *et al.* 2010b). Furthermore, panaxans seemed to have an influence on the immune-system and anti-tumor properties (Ni *et al.* 2010).

Studies on polyacetylenes (panaxynol, panaxydol):

Aliphatic C_{17} polyacetylenes of the falcarinol-type have been detected in the edible parts of many food plants belonging to the Apiaceae family, e.g. *Daucus carota*, *Apium graveolens*, *Pastinaca sativa*, *Foeniculum vulgare*, *Levisticum officinale* but also in ornamental and medicinal plants of the Araliaceae, e.g. *Schefflera arboricola*, *Hedera helix*, and *Panax ginseng*. In the last years several in-vitro studies showed a number of biological activities for falcarinol (=panaxynol) and falcarindiol, among them antimicrobial activity, anti-inflammatory and anti-platelet-aggregatory effects, neuroprotective activities, but also cytotoxic and anticancer effects. On the other hand, it has been demonstrated that falcarinol is an irritant and a potent contact allergen, being responsible for allergic and irritant skin reactions caused by *Hedera helix* (Christensen & Brandt 2006, Christensen 2011).

Antimicrobial activity (Kobaisy *et al.* 1997, Schinkovitz *et al.* 2008)

Falcarinol and other polyacetylens have been isolated from *Oplopanax horridus* and *Levisticum officinale* and showed antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Escherichia coli*, *Candida albicans*, *Mycobacterium tuberculosis*, *Mycobacterium avium*, *Mycobacterium fortuitum*, and *Mycobacterium aureum* with MICs of 16.4 µM (Mycobacteria), and 3.1-6.25 µg/ml (other bacteria and Candida). Differences in stereochemistry seemed to be of minor relevance regarding antibacterial activity.

Antiinflammatory and anti-platelet aggregatory activity (Teng *et al.* 1989, abstract only; Alanko *et al.* 1994, abstract only; Park *et al.* 1995, Fujimoto *et al.* 1998)

Falcarinol showed inhibitory effects on 5-Lipoxgenase (IC_{50} 2 µM), 12-lipoxygenase (IC_{50} 1µM), 15-lipoxygenase (IC_{50} 4µM) and on 15-hydroxyprostaglandin dehydrogenase (IC_{50} 25µM), which catalyses the initial step of prostaglandin catabolism. Its effect on various cyclooxygenases was marginal (IC_{50} >>100µM). In concentrations of 0.1 mg/ml falcarinol inhibited markedly the aggregation of washed platelets induced by collagen, arachidonic acid, ADP, ionophore A23187, PAF and thrombin via the inhibition of thromboxane B2 (a stable metabolite of thromboxane A_2) formation of platelets.

<u>Neuroprotective effects (Nie *et al.* 2006, Nie *et al.* 2008)</u>

Nie *et al*. (2006) investigated the protective effects of panaxynol and panaxydol on sodium nitroprusside induced neuronal apoptosis and potential mechanism of action in primary cultured rat cortical neurons. Cells were pretreated with panaxynol or panaxydol for 24 hours following exposure of 1 mM sodium nitroprusside for 1 hour. The treatment with the polyacetylenes resulted in a significant reduction of cell death. As a possible mechanism of action the regulation of the apoptotic related genes Bax and Bcl-2 is discussed.

In another experiment Nie *et al*. (2008) investigated the protective effects of panaxynol and panaxydol on Aβ25-35 induced neuronal apoptosis in primary cultured rat cortical neurons. Pretreatment of cells with panaxynol and panaxydol prior to 10 µM Aβ25-35 exposure resulted in a significant elevation of cell survival. Furthermore, the increase in calcium influx caused by Aβ25-35 was blocked by the polyacetylenes and both substances could also alleviate Aβ25-35-induced early-stage neuronal degeneration.

<u>Cytotoxic activity (Matsunaga *et al.* 1990, Zidorn *et al.* 2005, Yang *et al.* 2008, Yan *et al.* 2011)</u>

Matsunaga *et al*. (1990) investigated the cytotoxic effects of panaxynol, panaxydol and panxytriol on five different cell-lines (MK-1, B-16, L-929, MRC-5, and mesothelial cells). In order to increase water-solubility, solid complexes of the polyacetylene compounds with α-cyclodextrin had to be prepared. The ED_{50} values (growth inhibition) in normal cells were higher than in malignant cells. Treatment of MK-1 cells with polyacetylenes prior to incubation in fresh culture medium inhibited the cell growth significantly although cell viability was not affected. The cell growth inhibition seemed to be dose-dependent indicating cytostatic effects in low doses and cytotoxicity in high doses.

Zidorn *et al*. (2005) investigated the effects of falcarinol (panaxynol), falcarindiol, panaxydiol, and 8-O-methylfalcarindiol isolated from dichloromethane-extracts of roots and bulbs of different Apiaceae (carrot, celery, fennel, parsley, parsnip). In the annexin V-PI assay all investigated polyacetylenes showed medium-level cytotoxicity against the investigated leukemia, lymphoma, and myeloma cell lines with IC_{50} values of approximately 30 µM. Only falcarinol showed much higher activity against CEM-C7H2 cells with an IC_{50} value of 3.50 µM. Colorectal carcinoma cell lines were less sensitive to polyacetylenes in general with IC_{50} values above 100 µM.

Yang *et al*. (2008)investigated several polyacetylenes, among them panaxynol for their cytotoxic activity against different human cancer cell lines (A549, SK-OV-3, SK-MEL-2, and HCT-15) using the SRB method. Panaxynol showed ED_{50} values (cell growth inhibition) ranging from 2.38 to 6.04 µM against the tested cell lines.

Yan *et al*. (2011) examined the antiproliferation and proapoptotic effects of panaxynol (2, 5, 30 µM) and panaxydol (5, 30 µM) on HL60 cells and give insight into the mechanism of action. The cell growth inhibition was determined by tryptan blue dye exclusion assays. Apoptosis of cells was revealed by morphological observation, analysis for nuclear DNA distribution and by annexin V-FITC/PI staining using flow cytometry. Panaxynol and panaxydol markedly inhibited the proliferation of HL60 cells in a time- and dose-dependent manner via an apoptotic pathway via proteolytic activation of PKCδ, caspase-3 activation and cleavage of poly(ADP-ribose)polymerase.

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

Data regarding herbal preparations

There are no data available regarding any of the herbal preparations listed in 2.1 and 2.2. However, data on a special TCM-derived preparation named "Shenmai", which is a combination mainly of *Panax ginseng* and *Ophiopogon japonicus*, is presented. This preparation is commonly used in China for the treatment of coronary atherosclerotic cardiopathy and viral myocarditis and should also raise tumor patient's immunity (Yu *et al* 2007).

Yu *et al.* (2007), Xia (2008)

Yu *et al*. (2007) investigated the plasma concentration of ginsenosides Rg_1, Rf, Re, Rd, and Rb_1 after intravenous "Shenmai" injection (1.0 ml/kg), in rabbits. It was observed that the speed of elimination of ginsenosides Rg_1, Rf, and Re was much faster than of ginsenosides Rd and Rb_1.

In the study of Xia *et al*. (2008) six Sprague-Dawley rats (200-230 g) received an injection of "Shenmai (5 ml/kg) via the tail vein. The major compounds of this injection, ginsenosides Rg_1, Re, Rd, Rb1, ophiopogonin D and digoxin were detected in plasma. The pharmacokinetic behaviour of the ginsenosides was found to be structure-related: ginsenosides Rg_1 and Re [20(S)-protopanaxatriol as basic structure] were eliminated quickly, whereas ginsenosides Rd and Rb_1 [20(S)-protopanaxadiol as basic structure] had a relatively long elimination $t_{1/2}$ of approximately 22h.

Data regarding isolated compounds (exemplary studies)

Zhou *et al.* (2011)

Zhou *et al*. (2011) conducted a pharmacokinetic study in six male Wistar rats (220-240 g). A mixture of ginsenosides (0.034 mg/ml Rh_1, 0.063 mg/ml Rg_2, 0.066 mg/ml Rg_1, 0.074 mg/ml Rf, 0.082 mg/ml Re, 0.189 mg/ml Rd, 0.215 mg/ml Rc, 0.249 mg/ml Rb_2, and 0.296 mg/ml Rb_1) was administered via the tail vain at a dosage of 5 ml/kg. Ginsenoside Rh_1 and Rg_2 were eliminated rapidly in plasma with $t_{1/2}$ less than 0.75h. Ginsenosides Rc and Rb_2 had a relatively long elimination with $t_{1/2}$ more than 26 h. For Rh_1, Rg_2, Rg_1, Rf and Re the plasma concentration was lower than the lower limit of quantification after 1.5 h, for ginsenoside Rd, Rc, and Rb_1 after 72 h. The results confirmed the previous studies by Yu *et al.* (2007) and Xia *et al.* (2008) showing different pharmacokinetic behaviours regarding metabolism and excretion for compounds with the 20(S)-protopanaxatriol and 20(S)-protopanaxadiol structures.

Li Liang *et al*. (2011)

The metabolism of 20(S)-protopanaxadiol (PPD) in mixed human liver microsomes and human hepatocytes was examined in the study by Li Liang *et al* (2011). In total, 24 metabolites were found, and four of them were subjected to structure elucidation and identified. The predominant metabolic pathway of PPD observed was the oxidation of the 24,25-double bond to yield 24,25-epoxides, followed by hydrolysis and rearrangement to form the corresponding 24,25-vicinal diol-derivatives and the 20,24-oxide form. Further sequential metabolites through hydroxylation and dehydrogenation were also detected. All of the phase I metabolites except one possess a hydroxyl group at C-25 of the side chain, which was newly formed by biotransformation. Two glucuronide conjugates were detected in human hepatocyte incubations, and their conjugation sites were tentatively assigned to the 25-

hydroxyl group. In conclusion, the study demonstrates that PPD is extensively metabolized in human liver microsomes and hepatocytes.

Sun *et al.* (2012)

Sun *et al*. (2012) investigated the pharmacokinetic properties of ginsenoside-Rd in rodents (351 healthy adult Kunming mice, male and female, 18-20 g or Wistar rats, 180-200 g). After intravascular administration with 20, 50 or 150 mg/kg ginsenoside Rd, the dynamic changes of its concentration in plasma were observed. The peak-concentrations of ginsenoside Rd in mice were all reached as early as 2 min post-intravenous administration. After that, the concentrations were rapidly decreased by around 70% within 1 h. 8-24 hours later, the plasma levels of ginsenoside Rd were reduced by more than 90% compared to the initial plasma concentrations. Similar patterns were found in the rats thus indicating a linear elimination. Tissue distribution was determined after injection of ^{3}H-labeled ginsenoside Rd. The substance rapidly reached the peak in plasma and was then distributed to various tissues, among which the highest concentration was observed in the lung, followed by liver, kidney, heart and intestine. The lowest concentration was detected in the brain, probably due to the blood brain barrier. At 24 hours, the ginsenoside Rd concentration in tissue was reduced nearly by 90%. After 24 hours, except liver, spleen and lung, the radioactivity was close to the background level. The urinary excretion of ^{3}H-labeled ginsenoside Rd in mice and rats within 24 h was 60.8% and 37.2% and within 48 h was 62.86% and 39.5% respectively. Faecal excretion in mice and rats within 24 h was 18.45% and 31.7% and within 48 h was 18.75% and 36.6%, respectively. The authors suggested that the low toxicity of ginsenoside Rd observed *in vivo* is also caused by its rapid elimination. Furthermore the results indicated that ginsenoside Rd was mostly eliminated through urinary excretion.

Zhao *et al.* (2012)

Zhao *et al*. (2012) investigated the pharmacokinetic profile of ginsenosides Rb_1, Rb_2, and Rb_3 in Sprague Dawley rats (200-220 g) after oral (50 mg/kg) and intravenous (10 mg/kg, through tail vein) administration. Blood samples were collected according to a protocol and analysed by LC-ESI-MS. The results of the parameter T_{max} indicated that the absorption of Rb_3 was the fastest and Rb_1 was the slowest in this study. The $t_{1/2}$ after intravenous administration indicated that the three ginsenosides are eliminated slowly *in vivo*, whereby the elimination of Rb_1 was the fastest and Rb_3 was the slowest in this study. The $AUC_{0\text{-}36h}$ value for Rb_1 following oral administration was about 10 times larger than that of Rb_2 and was nearly two times larger than that of Rb_3, suggesting that the absorption of Rb_1 in rats is much higher than Rb_2 and Rb_3. The bioavailability after oral administration was low for all three tested ginsenosides (0.78% for Rb_1, 0.08% for Rb_2, and 0.52% for Rb_3. The authors concluded that pharmacokinetic behaviour was related to structural characteristics of the ginsenosides, suggesting that ginsenosides with hexose and hydroxyl groups (e.g. Rb_1) could be better absorbed after oral administration than those with pentose groups (e.g. Rb_2, Rb_3) in the same glycosylation site.

Assessor's comment on 3.1. and 3.2:

Due to a number of in vitro and in vivo studies ginsenosides are claimed to be the active principle of Panax ginseng. The results of several pharmacokinetic studies in animals indicate that the bioavailability of ginsenosides after oral administration is rather low, but there are also large differences between different ginsenosides in their pharmacokinetic behaviour. It seems possible that ginsenoside-metabolites contribute substantially to the pharmacological effects of ginseng (see also 4.1.2).

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

Data obtained with a dry extract [DER 3-7:1, extraction solvent ethanol 40% V/V containing 4% ginsenosides (sum of Rb_1, Rb_2, Rc, Rd, Re, Rf, Rg_1, Rg_2) usually referred as G115], herbal preparation D:

Acute toxicity

Jenny (1982)

Jenny (1982) reported that in a previous study (Kaku *et al.* 1975, only abstract available) the acute toxicity had been established in mice for ginsenoside Rg_2 (LD_{50} of about 305 mg/kg bodyweight) and ginsenoside Rf (LD_{50} of about 1340 mg/kg bodyweight) after i.p-administration. Previous studies on G115 (Trabucchi 1971, Berté 1973) revealed that the LD_{50} was not determinable in mice, rats or mini-pigs after oral administration and an LD_{50} of > 1000mg/kg b.w. p.o. was suggested. In the study by Jenny doses of 0, 250 mg, 500 mg, and 2000 mg/kg b.w. p.o. of G115 as well as doses of G115 without ginsenosides were tested in mini-pigs. All animals survived the tests without showing any other symptoms than a slight sedative effect, so that it was impossible to determine the p.o. LD_{50}. The intravenous injection of 1 mg/kg b.w. in mini-pigs caused an initial drop in blood pressure followed by a reduction in cardiac output and arrhythmia accompanied by convulsions, grinding of teeth and a reddening of the skin. These reaction could be prevented by H_2- and H_1-blocker, thus the author concluded that the observed side effects were due to a histamine-like substance or a histamine liberator.

Berté (1982)

Berté (1982) investigated the acute toxicity of G115 in mice, rats and mini-pigs and determined an LD_{50} of >5000 mg/kg p.o and >1000 mg/kg i.p. for mice (only one female mouse died after 1000 mg/kg). In mini-pigs a dose of 2000 mg/kg p.o. did not show any toxicological effect. No sudden death occurred, and during the 7-day follow-up no changes in body weight and blood parameters were detected.

Repeated dose toxicity

Jenny (1982)

It is reported that in a previous study (Savel 1971) rats tolerated a dose of 4000 mg/kg bodyweight p.o. of G115 for 20 days without showing any changes. Rabbits tolerated 80 mg/kg bodyweight p.o. of G115 over 100 days without any signs of toxicity. According to another study (Trabucchi 1971) rats and mice tolerated 40 mg/kg p.o. of G115 per day over two generations without showing any changes. On the other hand a report that observed a slight weight increase in rats after 10 mg/kg b.w. G115 p.o. over 15 days is mentioned. According to another study (Hess *et al.* 1983) G115 was administered to beagle dogs at dose levels of 1.5, 5 and 15 mg/kg b.w. over 90 consecutive days and showed no signs of toxicity.

Stevens & Cox (1978)

Subchronic and chronic toxicity of G115 were evaluated in a study on male and female purebred Beagle dogs following dietary administration for 90 consecutive days at doses of 0, 1.5, 5.0, and 15 mg of extract/kg body weight. Clinical, biochemical and hematological parameters were measured at initiation, 1 month and 13 weeks. Body weights and food consumption were measured weekly and upon termination. All animals were subject to necropsy, organs weighed and examined grossly and microscopically. Throughout the study treated animals did not differ significantly from untreated animals in any parameters examined. Treatment with G115 did not give evidence on any toxicological effects in Beagle dogs at doses up to 15 mg/kg/day.

Genotoxicity

Timm (1989, project report)

The extract G115 was subjected to an Ames-test using the *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100.The test was performed in 1989 in accordance with the OECD Guidelines for Testing Chemicals, Section 4, No. 471, "Salmonella typhimurium, Reverse Mutation Assay", adopted 1983, which were regarded valid at that time, and following the respective GLP regulations. The assay was performed in two independent experiments, both with and without liver microsomal activation (S9 mix) using five different concentrations (10.0, 100.0, 333.3, 1000.0, and 5000.0 µg /plate). The dry extract was dissolved in purified water, and each concentration, including the controls, was tested in triplicate. Concurrent untreated and solvent controls were performed as negative controls. Sodium azide (TA 1535, TA 100; 10µg/plate) and 4-nitro-o-phenylene-diamine (TA 1537, TA 1538, TA 98; 50µg/plate) served as positive control in the assay without metabolic activation. 2-aminoanthracene (10 µg/plate) was used in all strains as positive control in the assay performed with metabolic activation. The strains were derived from *Salmonella typhimurium* strain LT2 and checked regularly for their properties as well as for their normal spontaneous mutation rates. The S9 liver microsomal fraction was obtained from the liver of 8-12 weeks old male Wistar rats (weight 150-200 g) which received a single i.p. injection of 500 mg/kg b.w. Aroclor 1254 in olive oil 5 days previously. To evaluate the toxicity of the extract G115 and for purpose of dose-selection a pre-study with eight concentrations (3 plates each) was performed with strains TA 98 and TA100. Two % Vogel-Bonner-Glucose-Minimal-Agar was used as selective agar. The overlay agar contained histidine and biotine. The test solution, solvent control, positive- or negative control were mixed with the S9 mix or S9 substitution buffer, the bacteria suspension and the overlay agar and poured onto the selective agar-plates. After solidification the plates were incubated for 72 hours at 37°C in the dark. After incubation, the colonies were counted automatically, in case of precipitation of the test solution the revertant colonies were counted by hand. The generally accepted conditions for the evaluation of the results were the corresponding background growth on both negative control and test plates as well as the normal rate of spontaneous reversion rates for each strain. The test-substance was considered positive if either a significant dose-related increase in the number of revertants or a significant and reproducible increase for at least one test concentration had been induced. If neither a significant dose-related increase in the number of revertants nor a significant and reproducible positive response at any one of the test points had been observed the test substance was considered non-mutagenic in this system. A response was considered significant if in strain TA 100 the number of reversions was at least twice as high and in the other tested strains was at least three times higher as compared to the spontaneous reversion rate. Furthermore, a dose-dependent increase in the number of revertants was regarded as an indication of possibly existing mutagenic potential.

The plates incubated with G115 showed normal background growth up to 5000.0 µg/plate with and without S9 mix in all strains used. Up to the highest investigated concentration, no significant and reproducible dose-dependent increase in revertant colony numbers was obtained in any of the *Salmonella typhimurium* strains used. The presence of liver microsomal activation did not influence these findings. It is concluded that during the described mutagenicity test and under the experimental conditions reported, the extract G115 did not induce point mutations by base pair changes or frameshifts in the genome of the strains used.

Assessor's comment:

The study was well performed giving detailed descriptions of the materials and methods applied in the experiments as well as the evaluation of the assay. The only drawbacks are, with respect to the current version of the OECD guideline 471, that one strain is missing (TA 102) and that the number of cells per culture is not given.

Reproductive toxicity:

Trabucchi (1971, Investigational report)

40 mg G115 was given orally to pregnant Wistar-rats and New Zealand rabbits. The test preparation was administered by an intragastric tube to the rats (n=14) from the first day after mating to day 15 and to the rabbits (n=8) from day 7 to day 15 after mating. On day 21 for the rats and on day 27 for the rabbits, the foetuses were extracted by Caesarean section, counted, weighed and studied morphologically. The main internal organs were examined, as well as the foetal annexes and the presence of possible resorptions. No signs of abnormality in foetal development have been observed following the application of G115 under these experimental conditions.

Hess *et al.* (1982)

A study on reproductive toxicity was conducted in two generations of male and female Sprague-Dawley rats (160-180 g) with G115 administered at dose levels of 1.5, 5 and 15 mg/kg b.w. After 3 weeks of feeding the respective diets all of the rats in the F0 generation were paired. The number of pregnant females, number of pups born alive or dead, and survival of progeny were considered as parameters of reproductive performance. Two males and two females within each litter were selected for a further 13-week repeated dose feeding study, the other animals were sacrificed and gross autopsies were performed. After 13 weeks of feeding, the F1 generation rats were paired. Female F1 rats were fed their respective test diet throughout mating, gestation and lactation. Pregnant F1 females were allowed to deliver normally to produce the F2 generation. When the F2 pups were 21 days old, both they and the F1 animals were killed and autopsied. No significant evidence of toxicity or pathological effects was observed in the reproductive performance of two generations of male and female rats fed G115 at levels up to 15 mg/kg body weight per day.

Data obtained with a dry extract [extraction solvent Ethanol 80% containing 7.4 – 10.9% ginsenosides (sum of Rg_1, Re, Rf, Rb_1, Rc, Rb_2, and Rd)]

National Toxicology Program (2011), Chan *et al.* (2011)

A *Panax ginseng* root dry extract (extraction solvent EtOH 80%, not stated if V/V or m/m, DER not known) containing 7.4 and 10.9% ginsenosides (sum of Rg_1, Re, Rf, Rb_1, Rc, Rb_2, and Rd, differences due to different batches) was selected for testing in the US National Toxicology program (NTP TR 567). Studies on repeated dose toxicity/carcinogenicity and genotoxicity were performed. Toxicity studies in animals were conducted in F344/N rats and B6C3F1 mice. Animals for the two-week and the three-month repeated dose toxicity studies were obtained at four weeks of age and quarantined for 11 days before the beginning of the studies. Animals for the two-year repeated dose toxicity/carcinogenicity testing were obtained at 6-7 weeks of age and were quarantined for 13-19 days before the beginning of the study. Doses were applied by gavage, full details on animal husbandry and treatment are provided in the report. Animals were weighed individually on the first day of testing, at sacrifice and at regular intervals throughout each of the studies. Twice daily the animals were observed for morbidity, death, and clinical signs of pharmacological and toxicological effects of the extract. Organ weights were determined for all surviving animals until the end of the study. For the two-year chronic toxicity/carcinogenicity studies, all animals received a complete necropsy examination, including those that died before the end of the study. All observed clinical parameters and procedures including the complete histopathologic evaluation are described in detail in the report. For the statistical evaluation suitable methods were applied. In the following paragraphs the results of the NTP-investigations are briefly reported.

Repeated dose toxicity:

2-week study in rats:

Groups of five male and five female rats were administered ginseng extract in 0.5% aqueous methylcellulose by gavage at doses of 0, 125, 250, 500, 1000 or 2000 mg/kg, 5 days per week for 16 days. All rats survived to the end of the study. Mean body weight gain of 2000 mg/kg males was significantly higher than that of the vehicle controls. There were no chemical-related gross or microscopic findings attributed to the administration of the ginseng extract.

2-week study in mice:

Groups of five male and five female mice were administered ginseng extract in 0.5% aqueous methylcellulose by gavage at doses of 0, 125, 250, 500, 1000, or 2000 mg/kg, 5 days per week for 17 days. All mice survived to the end of the study. The final mean body weight of 1000 mg/kg males was significantly lower than that of the vehicle controls. There were no significant chemical-related gross or histopathologic changes in dosed mice.

3-month study in rats:

Groups of 10 male and 10 female rats were administered ginseng extract in sterile water by gavage at doses of 0, 1000, 2000, 3000, 4000, or 5000 mg/kg, 5 days per week for 14 weeks. All rats survived to the end of the study. Mean body weights of all dosed groups were similar to those of the vehicle control groups. No lesions that were observed by gross or histopathologic examination were attributed to the administration of ginseng.

3-month study in mice:

Groups of 10 male and 10 female mice were administered ginseng extract in sterile water by gavage at doses of 0, 1000, 2000, 3000, 4000, or 5000 mg/kg, 5 days per week for 14 weeks. All mice survived to the end of the study. Mean body weights of all dosed groups were similar to those of the vehicle control groups. Although sporadic incidences of lesions were observed in the vehicle control and 5000 mg/kg groups, there were no chemical-related gross or microscopic findings in dosed mice.

2-year study in rats:

Groups of 50 male and 50 female rats were administered ginseng extract in sterile water by gavage at doses of 0, 1250, 2500, or 5000 mg/kg, five days per week for 104 to 105 weeks. Survival of 5000 mg/kg females was significantly less than that of the vehicle controls; however, the deaths were not attributed to the administration of ginseng because no histopathologic findings attributable to ginseng were found. Mean body weights of 5000 mg/kg females were less than those of the vehicle controls throughout the study. No increases in the incidences of neoplasms or nonneoplastic lesions were attributed to the administration of ginseng. The incidence of mammary gland fibroadenoma was significantly decreased in 5000 mg/kg females.

2-year study in mice:

Groups of 50 male and 50 female mice were administered ginseng extract in sterile water by gavage at doses of 0, 1250, 2500, or 5000 mg/kg, 5 days per week for 105 weeks. Survival of dosed groups was similar to that of the vehicle control groups. Mean body weights of dosed mice were similar to those of the vehicle controls. The incidence of alveolar/bronchiolar adenoma or carcinoma in male mice increased with a positive trend; however, the incidence in the 5000 mg/kg group was not significantly different from the controls. The incidence (38%) was slightly above the historical range of 24-32% for gavage studies but within the range of 14-40% for all the routes. Therefore, the effects observed were not considered related to ginseng treatment. No other treatment related increases in neoplastic lesions were observed in mice.

Furthermore in the 2-year studies no histopathologic changes were observed in the brain tissues and no neurological or behavioral symptoms were observed in rats and mice administered ginseng extract at a dose as high as 5000 mg/kg. Moreover no evidence of hormonal effects in rats or mice was observed.

Genotoxicity:

Ginseng extract was not mutagenic in either of two independent bacterial mutagenicity assays, each conducted with or without exogenous metabolic activation enzymes (S9 mix from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) in accordance with the current OECD guideline 471 ("Ames-Test"). Bacterial strains tested included *Samonella typhimurium* strains TA 97, TA98, TA100, TA102, TA104, and TA1535, as well as *E. coli* strain WP2 uvrA/pKM101. The extract was tested in 6 different concentrations, in the first study up to 3333 µg/plate, in the second study up to 10000 µg/plate.

Furthermore, no significant increases were seen in the frequencies of micronucleated erythrocytes in the peripheral blood of male or female B6C3F1 mice exposed for 3 months to 1000 to 5000 mg/kg ginseng via gavage (see 3-month studies described above).

Carcinogenicity:

Under the conditions of the 2-year gavage studies, there was no evidence of carcinogenic activity of ginseng extract in male or female F344/N rats or B6C3F1 mice administered 1250, 2500, or 5000 mg/kg. The incidence of mammary gland fibroadenoma was significantly decreased in 5000 mg/kg female rats.

Data obtained with isolated compounds

Systematic investigations of genotoxicity have not been performed on isolated compounds of *Panax ginseng.* However, data from various in-vitro pharmacological investigations of the cytoprotective effects of *Panax ginseng* extracts and isolated compounds indicate antimutagenic properties for *Panax ginseng* extracts (Panwar *et al.* 2005, Khalil *et al.* 2008), ginsenoside mixtures (Jeong *et al.* 2007, Zhang Q *et al.* 2008) and the isolated ginsenosides Rb_1, Rg_2, and Rg_3 [Poon *et al.* 2012 (abstract only), Ha *et al.* 2010, Zhang *et al.* 2009].

3.4. Overall conclusions on non-clinical data

Numerous studies on extracts, fractions and isolated compounds have been conducted in animal models and *in vitro*. Effects on the nervous system, metabolism, cardiovascular system, immune systems, sexual organs and skin have been detected. Such investigations show that ginsenosides are constituents with a broad set of biological activities e.g. cytoprotective effects, anti-inflammatory effects, antimicrobial effects, and anti-cancer effects in various cell culture models but also in animal experiments. Pharmacokinetic investigations on ginsenosides revealed an extensive metabolism by intestinal bacteria, therefore ginsenosides might be regarded as prodrugs, and it seems possible that metabolites, such as compound K, contribute to the pharmacological activities of ginseng. Studies on the mechanism of action of ginsenosides revealed that these compounds are regulators of different ion channels and influence expression of different proteins. In the last years also polysaccharides (panaxans) and polyacetylenes (panaxynol, panaxydol, panaxytriol) have been investigated *in vitro* and *in vivo* for their contribution to effects of *Panax ginseng*. Concentrations of isolated compounds applied in animal models are often higher than expected in the therapeutic application of ginseng. Nevertheless studies with oral application of ginsenosides support the plausibility of traditional use.

Data from formal toxicity studies are available for the special extract G115, a dry extract obtained by extraction with EtOH 40% V/V and a DER of 3-7:1 containing 4% ginsenosides and a dry extract obtained by extraction with EtOH 80% (no further details regarding extraction solvent and DER, content of ginsenosides 7.4 and 10.9%). For both extracts data on repeated dose-toxicity as well as on genotoxicity are available. The extract G115 was also investigated for acute and reproductive toxicity; data on carcinogenicity are available for the 80% ethanolic extract from a two-year repeated dose toxicity study. Due to the low toxicity of the extract G115 it was not possible to establish LD_{50}, thus the authors of one study suggested values of >5000 mg/kg b.w.p.o and >1000 mg/kg b.w. i.p in mice. The extract G115 was well tolerated in repeated dose toxicity studies in rats, mice, mini-pigs, rabbits, and beagle dogs at doses up to 4000 mg/kg b.w. p.o. Results were similar for the 80% ethanolic extract in the 2-year repeated dose toxicity/carcinogenicity studies: doses up to 5000 mg/kg b.w. p.o were well tolerated by rats and mice without showing any signs of carcinogenicity. Reproductive toxicity studies were conducted with the extract G115 in rats and rabbits without showing any signs of abnormal foetal development or any negative influence on reproductive performance.

An Ames-test performed with the 80% ethanolic extract fully complies with the current OECD guideline 471 and showed a negative outcome. Furthermore in a mouse peripheral blood micronucleus test no significant increases in the frequencies of micronucleated erythrocytes were observed. Also in the Ames-test performed with G115 in 5 different strains of *Salmonella typhimurium* no signs for mutagenic properties were detected under experimental conditions. Since the strain TA 102 was missing in the Ames-test the data on G115 are not completely in accordance with the current OECD guideline 471. Therefore, even though the study was well performed providing detailed descriptions of the materials and methods applied in the experiments as well as for the evaluation of the assay, the development of a Community List Entry is not proposed.

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

Data obtained with herbal preparation D (dry extract, DER 3-7:1, containing 4% ginsenosides, extraction solvent ethanol 40% V/V, usually referred as G115):

Immunomodulatory effects:

Scaglione *et al.* (1994)

The study was performed in order to investigate the effects of G115 on the activity of alveolar macrophages of patients suffering from chronic bronchitis in a controlled, single-blind design. Two groups of informed volunteers affected with chronic bronchitis (20 subjects per group) were respectively treated with G115 extract (100 mg/12 hours for 8 weeks) and placebo. The function of alveolar macrophages, collected by bronchoalveolar lavage before and after 4 and 8 weeks from the onset of treatment, was determined by measuring the phagocytic activity and killing power towards *Candida albicans*. The phagocytosis and intracellular killing significantly increased at the eighth week of treatment with G115. The authors stated that G115 was able to improve the immune response of alveolar macrophages in chronically compromised subjects and suggested that preparations such as G115 might play an important role in the prevention or therapy of infective or immunological respiratory disorders.

<u>Scaglione *et al.* (1990)</u>

The aim of this study was the evaluation of the effects on the immunomodulatory activities in humans by a controlled, double-blind study design with the standardized ginseng extract G115 vs. placebo in comparison with an aqueous *Panax ginseng* extract. Sixty healthy volunteers were included in the study and received either 100 mg of G115, 100 mg of an aqueous *Panax ginseng* extract or placebo every 12h for 8 weeks. Several immunological parameters were determined on leukocytes from venous blood before and the 4 and 8 weeks after the onset of the treatment. The results showed that both extracts were able to stimulate an immune response in man, differing only on some parameters. The phagocytosis increased already at the fourth week in the group treated with G115 whereas in the other extract group the rise appeared to be delayed to the end of the eighth week. The same observation was made with T helper cells. Furthermore an enhancement of the T4/T8 helper cells ration was found in the G115 treatment group. Due to several other immunological findings the authors concluded that G115 was not only more active than the aqueous extract but also influenced a higher number of cell subsets belonging to the immune system.

<u>Cognition and cerebrovascular function:</u>

<u>Kennedy *et al.* (2003)</u>

Kennedy *et al*. (2003) investigated the electroencephalograph effects of single doses of *Ginkgo biloba* (GK 501) and *Panax ginseng* (G 115) extracts in a double-blind, placebo-controlled, balanced crossover experiment. Fifteen healthy volunteers (mean age 27 years) received single doses of 360 mg GK 501, 200 mg G 115 and an identical placebo. The auditory-evoked potentials, contingent negative variation (CNV), and resting power within the delta, theta, alpha, and beta wavebands were assessed on three separate occasions 4 h after consuming that day’s treatment. The order of presentation of the treatments was dictated by a Latin square with 7 days between testing sessions. The results showed that ginseng G115 led to a significant shortening of the latency of the P300 component of the evoked potential. Furthermore significant reductions in frontal “eyes closed” theta and beta, and alpha activity were observed. These findings showed that G 115 could directly modulate cerebroelectrical activity.

<u>Scholey & Kennedy (2002)</u>

Scholey & Kennedy investigated the acute cognitive effects of ginkgo (GK 501) and ginseng (G115) extracts and their combination in three studies. In the G115 study 20 healthy young adults (mean age 21 years) received either placebo, 200, 400, or 600 mg of G115. The participants had to attend a total of 5 study days, each followed by a wash-out period of 7 days. Testing sessions took place 1, 2.5, 4, and 6 h following administration of the day’s treatment. Each testing session included the completion of computerised versions of serial subtraction tasks (Serial Sevens, Serial Threes) with duration of 2 minutes. Different doses of ginseng improved accuracy and slowed responses during Serial Sevens but had no effect on Serial Threes. The 400 mg dose produced a specific beneficial effect evincing a significant reduction in errors at both the 4 and 6 h testing sessions on Serial Sevens. These findings were in line with previous findings where ginseng was associated with an improved “quality of memory”.

<u>Quiroga & Imbriano (1979)</u>

Quiroga & Imbriano (1979) investigated the effect of the *Panax ginseng* extract G115 on 200 patients, 157 were suffering from arteriosclerotic cerebrovascular circulatory insufficiency. The patients were classified in three groups according to the degree of circulatory insufficiency. All patients received 1 g of G115 per day for the first month and then 500 mg per day for the following two months to complete an investigation period of 90 days. Rheoencephalographic controls were made prior to the treatment and after 7, 15, 30, 60 and 90 days. 33% of the patients failed to attend the final examination after 90 days, so the final examination included only 134 patients. 36% experienced an improvement of more than 60% in circulatory insufficiency compared to the pre-treatment value, resulting in a recovery to almost normal state after 30 days of treatment, which remained constant after 60 days and 90 days. 54% of patients experienced an improvement of approximately 30% in the cerebral flow in comparison with the pre-treatment values and about 10% showed no or only short-lasting improvement.

Assessor's comment: The study was not double-blind with only 20 patients receiving placebo and is therefore of limited value.

Miscellaneous:

Engels *et al.* (2003)

The efficacy of G115 on secretory immunoglobulin A (SIgA), exercise performance, and recovery from repeated bouts of strenuous physical exertion was investigated by Engels *et al*. (2003) in a double-blind, placebo-controlled, randomized study including 38 active healthy adults. Participants received either 400 mg per day of G115 or placebo (lactose) for 8 weeks. Before and after the intervention each participant performed three consecutive 30s Wingate tests interspersed with 3 min recovery periods under controlled laboratory conditions. SIgA secretion rate and the relation of SIgA to total protein were calculated from measures of saliva flow rate, and absolute SIgA and salivary protein concentrations in timed, whole unstimulated saliva samples collected before and after exercise testing. Of the 38 subjects initially enrolled in this trial, 11 failed to complete one or more basic requirements according to the study protocol, only 27 completed the study. Compared with rest, SIgA secretion rate, SIgA:protein ratio and the saliva flow rate were lower after exercise than at baseline. Similarly, both peak and mean mechanical power output declined across consecutive Wingate tests. Postintervention minus preintervention change scores for salivary parameters, exercise performance, and HRR were similar between ginseng- and placebo-treated groups. The authors concluded that prolonged dietary intake of G115 did not affect mucosal immunity as indicated by changes in secretory IgA at rest and after an exercise induced state of homeostatic disturbance. Moreover, supplementation with G115 failed to improve physical performance and heart rate recovery of individuals undergoing repeated bouts of exhausting exercise.

Caron *et al.* (2002)

The aim of this prospective, randomized, double-blind, placebo-controlled study was to determine whether G115 ingestion can acutely or chronically alter electrocardiographic parameters, as well as blood pressure and heart rate. Thirty healthy adults were allocated to receive 28 days of treatment with either 200 mg of G115 or placebo. Baseline 12-lead electrocardiograms (ECG) were obtained Subsequent ECGs were performed following study drug ingestion at 50 min, 2 h, and 5 h on days 1 and 28. Blood pressure readings were taken with each ECG. G115 ingestion increased the QT_c interval by 0.015 seconds on day 1 at 2 hours compared with the placebo group. It also reduced diastolic blood pressure at the same time point No other statistically significant changes were found in electrocardiographic of hemodynamic variables on days 1 and 28. The authors stated that the observed effects were not believed to be clinically significant

Von Ardenne & Klemm (1987)

Von Ardenne & Klemm (1987) investigated the effect of G 115 on arterial and venous Hb-O_2 saturation in 16 elderly subjects receiving 200 mg G 115 per day for a period of four weeks. Increases in the resting pO_2 (partial oxygen pressure) uptake and in the O_2 transport into the organs and tissues of the body, from 100% before to 129% after the treatment were observed. The authors concluded that patients with an above-average loss of vitality are likely to derive greater benefit from the treatment than young healthy people.

Data on isolated constituents of *Panax ginseng*:

Liu H *et al.* (2009)

The efficacy and safety of ginsenoside Rd as a neuroprotectant in acute ischaemic stroke was investigated in a randomized, double-blind, placebo-controlled phase II multicentre trial. The study involved five major metropolitan general hospitals in China (provinces Shaanxi, Gansu, Yunnan, and Chongqing). A total of 199 patients were randomized equally to receive an infusion of placebo, ginsenoside Rd 10 mg or ginsenoside 20 mg per day for 14 days. The primary end-points were National Institutes of Health Stroke Scale (NIHSS) scores at 15 days. Secondary end-points were NIHSS scores and the Barthel Index at 8 days, the Barthel Index and the modified Rankin scale at 15 days and 90 days. The safety end-points included serious and non-serious adverse events, laboratory values and vital signs. For the primary study outcome, there was significant difference between the three groups at 15 days in NIHSS scores (P=0.0003). Comparing placebo with 10 mg/day and placebo with 20 mg/day, the difference in the mean for NIHSS was significant (P=0004, P=0009), but there was no significant difference between 10 mg/day and 20 mg/day. For the secondary study outcome, ginsenoside Rd did not improve neurological functioning. The incidence of serious and non-serious adverse events was similar among the three groups. The authors mentioned several limitations in this trial and suggested further investigations to validate the results in a phase III trial. However, they concluded that ginsenoside Rd might have some benefit in the management of acute ischaemic stroke.

Reeds *et al.* (2011)

The purpose of this randomized, double-blind, placebo-controlled study was to determine whether ginseng or ginsenoside Re improves β-cell function and insulin sensitivity in insulin-resistant subjects. Fifteen overweight or obese subjects (BMI=34±1; 1 man, 14 women) with impaired glucose tolerance or newly diagnosed type 2 diabetes were randomized to 30 days of treatment with ginseng root extract (8 g/day), ginsenoside Re (250-500 mg/day), or placebo. β-Cell-function was assessed as the disposition index and measured by a frequently sampled oral glucose tolerance test, and insulin sensitivity was assessed as the relative increase in glucose disposal during a hyperinsulinemic-euglycemic clamp procedure plus stable isotope tracer infusion. Values for disposition index and insulin sensitivity were not different before and after therapy in any of the three groups. Furthermore, ginsenosides Re, Rb_1, and Rb_2 were not detectable in plasma (detection limit 8 ng/ml), neither after treatment with ginseng root extract nor ginsenoside Re. The authors concluded that ginsenoside Re is poorly absorbed after oral ingestion and therefore limited in its therapeutic efficacy.

Lu *et al.* (2008)

The aim of the prospective, randomized, controlled study was to explore the effect and mechanism of ginsenoside Rg_3 on the postoperative life span of patients with non-small cell lung cancer (NSCLC, stage II-III, 3 to 6 weeks after radical operation). One hundred and thirty-three patients with NSCLC were randomly assigned to 3 groups receiving ginsenoside Rg_3, ginsenoside Rg_3 plus chemotherapy or only chemotherapy. Ginsenoside Rg_3 was applied orally at doses of 40-50 mg/day for at least half a year. The survival rates, immune function and the correlation between vascular endothelial growth factor expression and clinical effect were analysed in the three groups. There was no significant.difference between the three groups in 1-, 2-, and 3-year survival rate, although groups treated with ginsenoside Rg_3 showed slight advantages. The immune function was improved in the ginsenoside Rg_3 group and the combined group, showing an increased activity of NK cells and CD4 cells and normal levels in the ratio of CD4/CD8 cells.

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

Data obtained with herbal preparation D (dry extract, DER 3-7:1, containing 4% ginsenosides, extraction solvent ethanol 40% V/V, usually referred as G115):

<u>Tawab *et al.* (2003)</u>

In the study the degradation of ginsenosides in humans after oral administration was investigated. 700 mg of the extract G115 were taken orally as a single dose on an empty stomach by two healthy volunteers. Blood and urine samples were taken according to a defined protocol and screened for the presence of ginsenosides and their metabolites by LC-ESI-MS. In the extract Rg_1, Rb_1, Rb_2, Rc, Rd, Re and Rf were detected representing the protopanaxadiol as well as the protopanaxatriol type of ginsenosides. In the first 5 hours after application the monoglucosylated ginsenoside Rh_1, the main hydrolysis product of ginsenoside Rg_1, was detected in plasma. At later timepoints Rb_1, Rf_1 and compound K were detected as well. In urine in the first 3 hours the intact ginsenosides Rg_1, Rd, Re, Rb_2, and Rc were detected. From 3-6 hours after drug administration only compound Rh_1 has been detected, at later timepoints Rb_1, RF_1, Rh_1, and compound K. It is known that the metabolism of ginsenosides proceeds mainly via degradation processes already occurring in the gastrointestinal tract caused either by gut microorganisms, intestinal enzymes or gastric fluid. The rapid absorption of Rh_1 wasis an indication for the hydrolysis of Rg_1 occurring in the stomach. The reappearance of Rh_1 8 hours after drug administration might be ascribed to different pathways as suggested by Tawab *et al*. (2003, see **Fig. 3**). Unchanged Rg_1 might be hydrolysed by intestinal bacteria to RF_1 as observed by *in vitro* incubation with fecal cultures (Hasegawa 1996, only abstract available). Re might be hydrolysed in stomach to yield Rg_2 and then be converted to Rh_1 through intestinal bacteria. Unhydrolized Re might be metabolized by intestinal bacteria to RF_1 via Rg_1. In general mainly the monoglucosylated degradation products of the protopanaxatriol ginsenosides had been absorbed and not the corresponding aglycones. No degradation products of the protopanaxadiol ginsenosides (mainly compound C) were detected in plasma and urine in the early hours after administration, suggesting that protopanaxadiol ginsenosides are hardly decomposed in the stomach. This finding indicated that the degradation of protopanaxadiol ginsenosides and the absorption of compound K took place in the lower part of the intestine. The detection of the intact ginsenosides Rg_1, Rd, Re, Rb_2 and Rc in urine but not in plasma was ascribed to the lower limit of detection observed in urine by the authors. It was proven that two degradation products of the protopanaxatriol ginsenosides (Rh_1 and RF_1) may reach the systemic circulation in humans in addition to compound K. Rb_1 could be clearly identified in plasma and urine. As this was a pilot study including only two volunteers the authors concluded that further experiments should be conducted in order to better understand the molecular mechanism of action and clinical effects of ginsenosides.

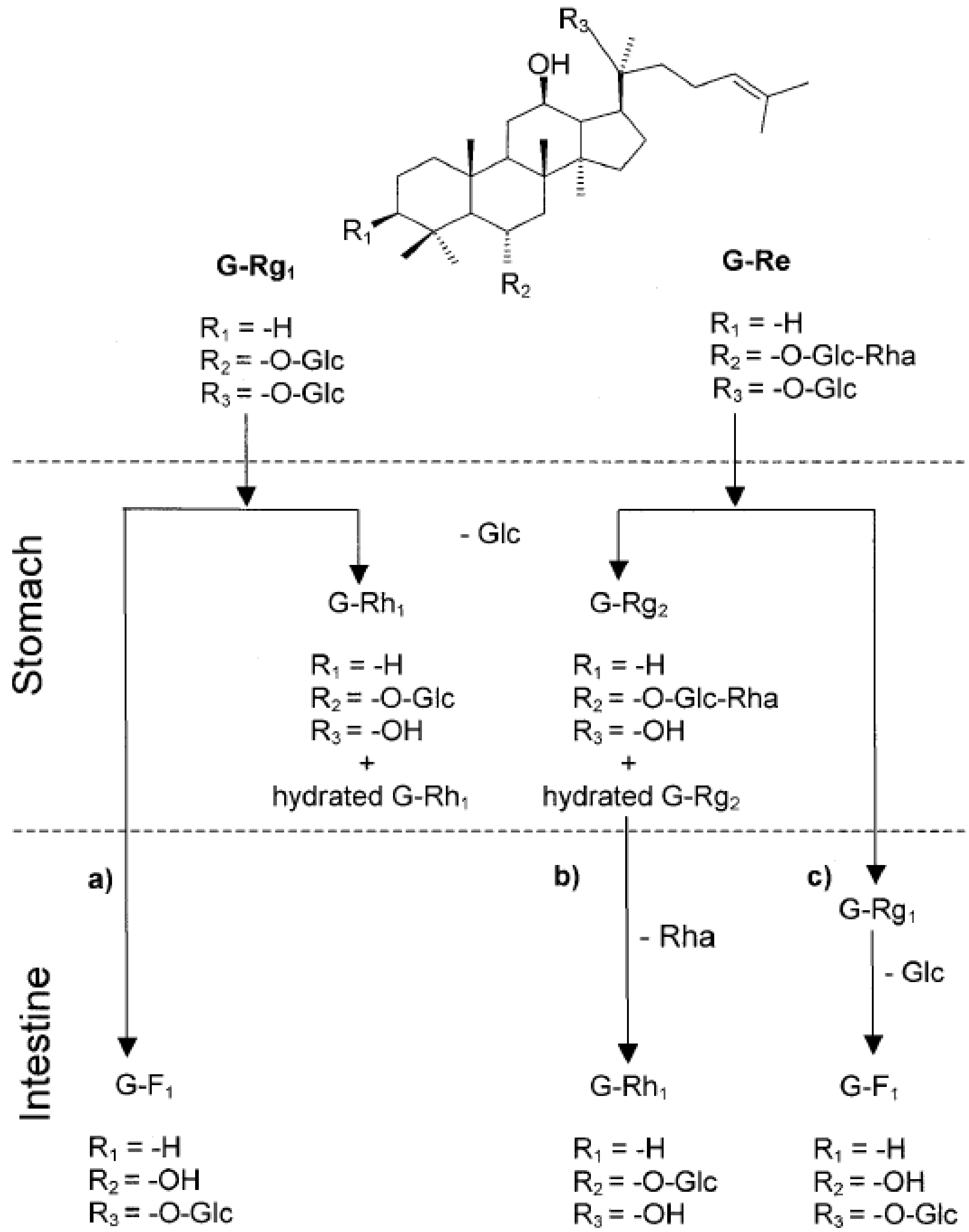


Fig.3: Tawab *et al.* (2003): Possible degradation pathway of ginsenosides Rg_1 and Re

Ginsenoside Rd

Zeng *et al.* (2010)

The pharmacokinetics and safety of ginsenoside Rd were assessed in 24 healthy Chinese volunteers in a phase I randomized, open-label, single- and multiple dose study. In the single dose, randomized, open-label, 3-way crossover study 12 participants were assigned to receive 10, 45 or 75 mg Rd by intravenous infusion, with a 2-week washout period between dosing periods. Plasma-levels of ginsenoside Rd were found to be proportional to dose, with the mean C_{max} and $AUC_{0-\infty}$ ranging from 2.8 to 19.3 mg/L and 27.9 to 212.5 mg*h/L over the dose range studied. Ginsenoside Rd was slowly cleared from plasma ($t_{1/2Z}$=17.7-19.3 hours). In the multiple-dose study, 10 mg ginsenoside Rd was administered once daily for 6 days to 12 participants. The mean steady-state C_{max}, $AUC_{0-\infty}$ and AUC_{ss}

were 4.0 mg/L, 51.7 mg*h/L, and 26.4 mg*h/L, respectively. The $t_{1/2Z}$ was 20.5 hours, which was similar to the single-dose value. Ginsenoside Rd displayed linear pharmacokinetics in the dose range of 10 to 75 mg after single intravenous doses. As the compound is slowly cleared from plasma after multiple doses ginsenoside Rd accumulated slightly, but the elimination rate did not show any changes. Adverse events included increases in alanine aminotransferase (ALT) and blood urea nitrogen (BUN) and decreases in diastolic blood pressure (DBP), white blood cell counts and heart rate, which were mild in intensity and did not appear to be dose-related. Among those, the adverse events found in two participants were considered to be clinically meaningful changes and were judged possibly related to the study drug by the investigator resulting in a withdrawal from the study. No serious adverse events were reported in the multiple-dose study, however of the 12 enrolled participants, 4 discontinued from the study. In general, ginsenoside Rd was considered to be well tolerated in the study doses range.

Ginsenoside Rg_1

Yang L *et al.* (2009)

The pharmacokinetic profile of ginsenoside Rg_1 following intravenous “Shenmai” infusion (*Panax ginseng* and *Ophiopogon japonicus*) has been investigated in ten healthy Chinese volunteers (5 male, 5 female). Blood samples were taken according to a defined protocol and investigated by LC-ESI-MS/MS. The distribution half-life $t_{1/2\alpha}$ and the elimination half-life $t_{1/2\beta}$ for Rg_1 were 0.28 h and 2.09 h respectively, indicating that Rg_1 might be distributed and eliminated rapidly.

Qi *et al.* (2011)

Qi *et al*. (2011) published a review on pharmacokinetic data on ginsenosides. In general the intestinal absorption of ginseng saponins is limited due to extensive metabolism in the gastrointestinal tract (Tawab *et al.* 2003, Cai *et al.* 2003), poor membrane permeability (Liu X *et al.* 2009), and low solubility of degylcosylated products (Gu *et al.* 2009). The bioavailability of the protopanaxadiol group of saponins (i.e. ginsenosides Ra_3, Rb_1, Rd, Rg_3, and Rh_2) and of the protopanaxariol group of saponins (i.e. ginsenosides Rg_1, Re, Rh_1 and R1) was less than 5%. Protopanaxadiol saponins degrade faster than protopanaxatriol saponins, thus having a lower bioavailability. High doses may saturate metabolism and increase bioavailability. Tissue disposition showed that liver and bile clear ginsenoside-metabolites from circulation (Paek *et al.* 2006). Attachment of more sugar moieties in the protopanaxadiol ginsenosides Ra_3, Rb_1, Rc, and Rd blocked their access to biliary transporters and slowed biliary excretion. Most ginsenosides and their deglycosylated products were excreted by the biliary system through active transport (Liu X *et al.* 2009). Time curves of ginsenosides exhibited distinct multiple peaks after oral administration, indicating the involvement of enterohepatic recirculation (Paek *et al.* 2006). Approximately 0.2%-1.2% of ginsenosides was excreted in human urine (Cui *et al.* 1997).

Cui *et al.* (1996)

Urine samples of Swedish athletes which had consumed ginseng preparations within 10 days before urine collection were analysed. 20-(S)-protopanaxatriol was found in about 90% of the samples analysed. The concentrations of 20-(S)-protopanaxatriol-ginsenosides varied between 2 and 35 ng ml^{-1} of urine. As 20-(S)-protopanaxadiol-ginsenosides could hardly be traced in urine the authors concluded that their uptake, metabolism, and excretion differ from 20-(S)-protopanaxatriol-ginsenosides in man.

Lee J *et al.* (2009)

The study aimed to characterize the absorption, distribution and metabolism of ginseng in 34 healthy male human subjects using pharmacokinetic experiments based on the metabolism of intestinal microflora. To investigate whether large differences in each individual’s intestinal microflora metabolic ability resulted from differences in the composition of ginseng, fecal organisms were incubated with ginsenoside Rb_1 and ginseng extract (BuOH) *in vitro* to compare the ability of the microflora to metabolize ginseng into compound K. After oral administration of 12 g ginseng powder, blood samples were analysed to quantify the amount of compound K in blood plasma and the C_{max}, T_{max} and AUC were calculated. Compound K was absorbed into the blood 24 h after oral administration of ginseng powder, with average values of 10.76±2.07 h for T_{max}. 27.89±24.46 ng/ml for C_{max}, and 221.98±221.42 µg h/ml for AUC, respectively. The large variations in C_{max} and AUC between individuals are likely to be caused by variances in the transforming activity of the intestinal microflora from different individuals. There was a correlation between the compound K transforming activity of ginsenoside Rb_1 and the compound K transforming activity of ginseng extract by the intestinal microflora. The authors concluded that the absorption of the final metabolites of ginseng is independent from the metabolite transforming activity of the intestinal microflora, but the T_{max}, C_{max} and AUC of the transformed metabolites depend on the activity of each individual's microbial flora.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

According to an extensive literature search in Pubmed and other sources (see 1.3) several systematic reviews about the efficacy and safety of ginseng preparations in general (Lee & Son 2011, Vogler *et al.* 1999, Coon & Ernst 2002) as well as the efficacy of ginseng preparations in the following indications have been found:

- Cognitive function (Geng *et al.* 2010, Lee MS *et al.* 2009)
- Cardiovascular risk factors (Buettner *et al.* 2006)
- Stable chronic obstructive pulmonary disease (An *et al.* 2011)
- Prevention of common cold in healthy adults (Krebs Seida *et al.* 2009)
- Erectile dysfunction (Jang *et al.* 2008)

Numerous clinical investigations on the powdered roots of white and red ginseng (herbal preparations B and K), as well as on the dry extract containing 4% ginsenosides (herbal preparation D, often referred as G115) have been conducted since the 1950s and are discussed in the following section. No publications on clinical investigations have been found regarding the other preparations listed in 2.1. Further clinical studies on preparations other than those mentioned in 2.1 are listed in the table below but were not assessed, since the description of the preparations is considered not sufficient

Author, Year	Preparation
Ping *et al.* (2011)	*Panax ginseng*, no further information
Yi *et al.* (2009)	*Panax ginseng*, no further information
Yamamoto & Kumagai (1982, no abstract)	*Panax ginseng*, no further information
Bahrke & Morgan (1994, abstract only)	Ginseng, no further information
Chin (1991, no abstract)	Ginseng, no further information
Kim *et al.* (2009)	Mountain Ginseng extract, derived from tissue culture, no further information
Kulaputana *et al.* (2007, abstract only)	Ginseng, no further information
See *et al.* (1997)	Dried ground preparation of fresh herb, no further information
Salvati *et al.* (1996, abstract only)	*Panax ginseng* extract, no further information
Avakian & Evonuk (1979, abstract only)	*Panax ginseng* extract, no further information
Oh *et al.* (2010, abstract only)	Korean red ginseng extract, no further information

White ginseng, powdered herbal substance (herbal preparation B)

Effects on blood glucose level:

Ma *et al.* (2008)

Effects on biomarkers of glucose tolerance were studied in a randomized, placebo-controlled, double-blinded crossover study in 20 type 2 diabetes patients. Subject’s diabetes was controlled with diet and/or oral hypoglycaemic agents, which were continued throughout the study. After a 2-week placebo-controlled run-in period, subjects were randomized to take two capsules containing 369 mg ginseng powder three times daily or placebo for four weeks. Placebo capsules were then taken for two weeks as washout after which subjects crossed over to the other treatment for 4 weeks. At the end of the run-in and each 4-week treatment, subjects underwent a 75 g oral glucose tolerance test (OGTT). Plasma glucose, insulin and biomarkers of oxidative stress and antioxidant status were measured. Insulin resistance and fasting glucose decreased significantly within 4 weeks of ginseng treatment compared with placebo, but the glucose and insulin responses to the OGTT were not significantly changed. There were no significant changes in biomarkers of antioxidant defence or oxidant stress seen acutely in response to the OGTT or when comparing post-ginseng treatment with entry or with post-placebo.

Sievenpiper *et al.* (2003a) (see also Buettner *et al.* 2006)

The efficacy of *Panax ginseng* powder was investigated in two acute dose escalation studies each involving 11 healthy subjects (male and female) using a randomized, single-blind, placebo-controlled, multiple-crossover design. Treatments consisted of 0, 1, 2, and 3 g of *Panax ginseng* for the first study, and 0, 3, 6, 9 g for the second study. Doses were administered 40 minutes before a 75 g oral glucose tolerance test (OGTT). Neither the main effect of pooled-treatment, nor dose, nor either factors interaction with time was significant for incremental plasma glucose and insulin. The two-hour plasma glucose value was significantly higher for pooled Asian ginseng treatment than placebo, which was in contrast to previous findings in studies with American ginseng (*Panax quinquefoliu*s). The authors concluded that this finding might be due to variances in ginsenoside pattern of the different ginseng samples and suggested investigations of standardized preparations.

Sievenpiper *et al.* (2004)

A double-blind, randomized, multiple-crossover study was conducted to investigate the effects of various ginseng species on acute postprandial glycemic indices in 12 healthy participants. Commercial samples of *Panax ginseng* (red and white), *Panax quinquefolius* (wild and cultivated), *P. vietnamensis*, *P. japonicus*, *P. notoginseng* and *Eleutherococcus senticosus* were applied in 3 g doses 40 min prior to a 75 g oral glucose tolerance test. The samples showed considerable variances in ginsenoside profile and differential and contradictory effects on plasma glucose. *Panax ginseng* significantly increased incidences of acute postprandial plasma glucose and preprandial plasma insulin levels compared with placebo, whereas e.g. *Panax quinquefolius* showed the opposite effect.

Effects on cognitive performance:

Lee ST *et al.* (2008, only abstract available) (see also systematic reviews by Lee *et al.* 2009, Geng *et al.* 2010, Lee & Son 2011)

Lee ST *et al*. (2008) investigated the clinical efficacy of *Panax ginseng* in the cognitive performance of Alzheimer's disease (AD) patients in an open-label study. Consecutive AD patients were randomly assigned to the ginseng (n=58) or the control group (n=39) and the ginseng group was treated with *Panax ginseng* powder (4.5g/day) for 12 weeks. Cognitive performances were monitored using the mini-mental state examination (MMSE) and Alzheimer disease assessment scale (ADAS) during 12 weeks of the ginseng treatment and at 12 weeks after ginseng discontinuation. After ginseng treatment, the cognitive subscale of ADAS and the MMSE score began to show improvements and continued up to 12 weeks (P=0.029 and P=0.009 vs. baseline, respectively). After discontinuing ginseng, the improved ADAS and MMSE scores declined to the levels of the control group.

Red ginseng, powdered herbal substance (herbal preparation K)

Effects on blood glucose level:

De Souza *et al.* (2011)

A randomized, double-blind, placebo-controlled, multiple-crossover study including 16 healthy volunteers investigated the effects of Korean red ginseng root-body and rootlets on postprandial glycaemia. Rootlets and roots were examined for their content of ginsenosides showing a considerably higher amount for the rootlets. The Korean red ginseng treatments and the control (cornstarch) were dried, ground and encapsulated, each capsule containing 500 mg. Treatment consisted of 6 capsules, either 3 g Korean red ginseng root, rootlets or placebo, based on a previous dose-finding study equating the effects of 2-6 g doses. Treatments were consumed 60 min prior to the start of a standard test meal (12 g protein, 7 g fat, 51 g total carbohydrate) followed by blood sampling over two hours. The treatment with Korean red ginseng root body produced significant glycemic reductions across every individual postprandial time-point after 30 min and a tendency towards lower incremental peak glucose. Overall, there was a 27% reduction in AUC postprandial glucose levels compared to the control. In contrast, the treatment with rootlets was only negligibly different from control treatment. In contrast to previous studies, which investigated extracts of Korean red ginseng, here the crude drug was used for treatment. The authors concluded that further studies on well characterized extracts should be conducted and also other compounds than the ginsenosides might contribute to the Korean red ginseng's effect on blood glucose levels. Additionally, long-term administration of Korean red ginseng should be investigated.

Vuksan *et al.* (2008) (see also systematic review by Lee & Son 2011)

Nineteen participants with well-controlled type 2 diabetes were included in a double-blind, randomized, cross-over clinical study to investigate the effects of Korean red ginseng rootlets on glucose and insulin regulation. Each participant received in addition to the usual anti-diabetic therapy (diet and/or medications) either 2 g/meal (in total 6 g per day) of Korean red ginseng treatment or placebo (cornstarch) for 12 weeks. There was no change in the primary endpoint HbA_{1c}. The Korean red ginseng treatment decreased 75 g-oral glucose tolerance test (OGTT) plasma glucose indices by 8-11% and fasting plasma insulin and 75 g-OGTT plasma insulin indices by 33-38%. The authors concluded that although clinical efficacy (HbA_{1c}) was not demonstrated plasma glucose and plasma insulin regulation could be improved by treatment with Korean red ginseng.

Effects on cardiovascular function, blood pressure and blood lipids:

Rhee *et al.* (2011)

Rhee *et al*. (2011) investigated the effect of Korean red ginseng powder on arterial stiffness in subjects with hypertension. Eighty participants who were treated with antihypertensive agents were randomly assigned to an active (3 g Korean red ginseng per day) or a placebo treatment group in a double-blind manner. Participants had to continue their antihypertensive medication during the 3-month-study. Systolic and diastolic blood pressures were measured at baseline, 1, 2, and 3 months. Measurements were conducted three times at 5-minute intervals using an automated sphyngomanometer. An average calculated from two close readings was used for analysis. Arterial stiffness was assessed by the measurement of brachial-ankle pulse wave velocity at baseline, 1, 2, and 3 months. After three months of treatment systolic blood pressure was not changed from baseline in the active group. Diastolic blood pressure in both groups and systolic blood pressure in the placebo group were significantly reduced ($p<0.05$) after three months of treatment. Arterial stiffness was not improved by a three-month-treatment with Korean red ginseng.

Jovanovski *et al.* (2010,only abstract available)

The effects of Korean red ginseng, isolated ginsenosides, and polysaccharides on arterial stiffness have been investigated in healthy individuals. A total of 17 healthy fasted individuals were included in the randomized, controlled, double-blind crossover trial and received 3 g of either placebo, Korean red ginseng root, or a Korean red ginseng root bioequivalent dose of ginsenoside or polysaccharide fractions. Blood pressure and augmentation index, an emerging method to assess cardiovascular risk beyond conventional blood pressure measurements. Compared to placebo, 3 g of Korean red ginseng significantly lowered radial augmentation index by 4.6% ($p=0.045$), whereas the ginsenoside fraction comparably decreased augmentation index by 4.8% ($p=0.057$) and no effect was observed with the polysaccharides. There were no differences in blood pressure between treatments.

Sung *et al.* (2000) (only abstract available, see also review by Buettner *et al.* 2006)

Effects of red ginseng on vascular endothelial function in patients with essential hypertension were investigated by Sung *et al* (2000). A total of 17 patients with hypertension were divided into ginseng-treated and non-treated groups. Furthermore 10 normotensive volunteers were included. To assess the function of the vascular endothelial cell, changes of forearm blood flow to infusion of acetylcholine, sodium nitroprusside and bradykinin in incremental doses were measured by venous occlusion plethysmography. In the ginseng –treated hypertensive group, forearm blood flows at the highest dose of acetylcholine and bradykinin were significantly higher than those of the non-treated hypertensive group and were not different from those of the control group. In the case of sodium nitroprusside infusion, no significant differences were observed between the control, non-treated and treated groups. The authors concluded that Korean red ginseng could improve the vascular endothelial dysfunction in patients with hypertension possibly through increasing synthesis of nitric oxide.

Han *et al.* (1998) (only abstract available, see also review by Buettner *et al.* 2006)

The objective of this study was to evaluate the changes of diurnal blood pressure pattern after 8 weeks of red ginseng medication (4.5 g/day) by 24 hour ambulatory blood pressure monitoring. In 26 subjects with essential hypertension, 24 hour mean systolic blood pressure decreased significantly ($p=0.03$) while diastolic blood pressure only showed a tendency of decline ($p=0.17$). The decrease in pressures were observed at daytime (8 a.m – 6 p.m) and dawn (5 a.m to 7 a.m). In 8 subjects with white coat hypertension, no significant blood pressure change was observed. The authors suggested that red ginseng might be useful as an adjuvant to current antihypertensive medications.

Yamamoto *et al.* (1983) (only abstract available, see also review by Buettner *et al.* 2006)

Yamamoto *et al*. (1983) investigated the effects of *Panax ginseng* on plasma and hepatic lipids in high cholesterol diet-fed rats and patients with hyperlipidemia. Oral administration of red ginseng powder reduced plasma total cholesterol and triglyceride while HDL-cholesterol was elevated. Platelet adhesiveness was also reduced by ginseng administration. The plasma lipid-improving actions were also observed in patients with hyperlipidemia. Hepatic cholesterol and triglyceride contents were decreased and phospholipid increased by ginseng administration in the high cholesterol diet-fed rats, corresponding to improvement of the fatty liver.

Effects on erectile dysfunction:

De Andrade *et al.* (2007) (see also systematic reviews by Lee & Son 2011, Jang *et al.* 2008)

The aim of the study was to examine the treatment efficacy of Korean red ginseng in men with erectile dysfunction. A total of 60 patients presenting mild or mild to moderate erectile dysfunction were enrolled in a double-blind, placebo-controlled study receiving three times daily either Korean red ginseng or placebo. The five-item version of the International Index of Erectile Function score after 12-weeks treatment was significantly higher in the Korean red ginseng group compared with that before treatment ($p<0.0001$). In contrast, there was no difference before and after the treatment in the placebo group ($p>0.05$). Furthermore, there was a significant improvement in total score in questions 3 and 5 of the treatment group compared to placebo. Differences in the levels of serum testosterone, prolactine and cholesterol before and after the treatment were not statistically significant between the treatment and control group.

Hong *et al.* (2002) (only abstract available, see also systematic reviews by Lee & Son 2011, Jang *et al.* 2008)

A total of 45 patients with clinically diagnosed erectile dysfunction were enrolled in a double-blind, placebo controlled, cross-over study (8 weeks treatment, 2 weeks of washout and 8 weeks treatment) in which effects of Korean red ginseng and a vehicle placebo were compared using multiple variables. Treatment consisted of 900 mg Korean red ginseng three times daily. The efficacy of Korean red ginseng for erectile dysfunction was investigated using the International Index of Erectile Function, RigiScan, hormonal levels and penile duplex ultrasonography with audio-visual sexual stimulation. Mean International Index of Erectile Function scores were significantly higher in patients treated with

Korean red ginseng than in those who received placebo. Scores on questions 3 and 4 were significantly higher in the ginseng than in the placebo group. In response to the global efficacy question 60% of the patients answered that Korean red ginseng improved erection ($p<0.01$).

Choi *et al.* (1995) (only abstract available, see also systematic reviews by Lee & Son 2011, Jang *et al.* 2008)

A total of 90 patients were divided equally into a red ginseng treatment group, trazodone treatment group and placebo group. Changes in symptoms such as frequency of intercourse, premature ejaculation and morning erections after treatment were not changed in any of the three groups ($p>0.05$). In the group receiving ginseng, changes in early detumescence and erectile parameters were significantly higher than that of the other groups ($p<0.05$) The overall therapeutic efficacies on erectile dysfunction were 60% for ginseng group and 30% for placebo and trazodone treated groups, statistically confirming the effect of ginseng ($p<0.05$). No complete remission of erectile dysfunction was noted but partial responses were reported. No cases of aggravation of symptoms were reported. AVS-penogram, which is a recording of penile hemodynamic, changed during the natural erection after audio-visual stimulation, was not changed after administration of ginseng. The authors concluded that the administration of Korean red ginseng was shown to have superior effects compared to placebo or trazodone but more research is required.

Effects on quality of life:

Kim *et al.* (2006)

The objective of this study was to investigate the effects of “sun ginseng” (heat processed ginseng) on subjective quality of life in cancer patients. A randomized, double-blind, placebo-controlled pilot trail was performed for 12 weeks, including 53 patients who received either 3 g/day of ginseng or placebo. Patient’s diagnosis were gynaecologic cancer (n=53), hepatobiliary cancer (n=13) and other cancers (n=12). Quality of life was assessed using the WHO Quality of Life Assessment-Bref (WHOQOL-BREF) and the General Health Questionnaire-12 (GHQ-12). After 12 weeks of therapy, the “psychological domain” score of the WHOQOL-BREF was significantly improved in patients randomized to ginseng, compared with those of placebo ($p=0.02$). There was a tendency for ginseng to improve the “physical health” ($p=0.06$) and “environment” ($p=0.07$) domain scores of the WHOQOL-BREF compared to placebo. The GHQ-12 total score was significantly improved in patients treated with ginseng compared to placebo ($p<0.01$). No significant adverse events were observed in both groups of patients. The authors concluded that “sun ginseng” was found to be beneficial in improving some aspects of mental and physical functioning after 12 weeks of therapy in gynaecologic and hepatobiliary cancer patients, but further studies are required to evaluate the long-term effects on multiple facets of quality of life in larger samples of various cancer patients.

Effects on cognitive impairment:

Heo *et al.* (2008) (see also the systematic review by Lee MS *et al.* 2009, Geng *et al.* 2010, Lee & Son 2011)

Sixty-one patients (24 males and 37 females) with Alzheimer’s disease (AD) were randomly assigned to low-dose Korean red ginseng group (4.5 g/day), high dose Korean red ginseng group (9 g/day) or control. All participants had been treated with either donepezil (5-10 mg/day), galantamine (16-24 mg/day), memantine (20 mg/day) or rivastigmine (6-12 mg/day) for at least 6 months before randomization, and the medication was continued during the ginseng-study. The Alzheimer’s Disease Assessment Scale (ADAS), Korean version of the Mini-Mental Status Examination (K-MMSE) and

Clinical Dementia Rating (CDR) scale were used to assess the change in cognitive and functional performance at the end of the 12-week study period. The patients in the high dose-group showed significant improvement on the ADAS and CDR after 12 weeks compared with those in the control group (p=0.032 and 0.006, respectively). Both treatment groups showed improvement from baseline MMSE in comparison to the control group but this improvement was not statistically significant. No statistically significant difference in adverse events was found between the three treatment groups. The authors admitted several limitations of the study, such as the small number of study subjects or the rather short study duration. Furthermore, the possibility of a placebo effect could not be excluded because the study was not blinded. Nevertheless, the authors concluded that Korean red ginseng showed positive effects on cognitive improvement and might be beneficial as an adjuvant treatment for AD patients.

Miscellaneous:

Sung *et al.* (2005)

Sung *et al*. (2005) investigated the effects of Korean red ginseng intake on CD4 T cells, sCD8 and HLA (Human leucoycte antigen) prognostic score. Ninety HIV-1-infected Korean patients diagnosed from 1987 to 2001 had been recruited and were asked to return for an interview and for a clinical examination and a blood sample every 6 months. 68 of the HIV-1 infected patients had lived for more than 5 years without antiretroviral therapy. 61 of these patients received Korean red ginseng (4.082±3.928 g daily) over 111.9±31.3 months. Data analysis showed that there were significant inverse correlations between the HLA prognostic score and annual decrease in CD4 T cells. In addition Korean red ginseng intake significantly slowed the decrease in CD4 T cells even when the influence of HLA class 1 was statistically eliminated. Furthermore a significant correlation between Korean red ginseng intake and a decrease in serum-soluble CD8 antigen level was observed. The authors concluded that Korean red ginseng intake independently has beneficial effects on the slow decrease in CD4 T cells and on serum sCD8 levels in HIV-1 infected patients although the HLA factor was also significantly associated with the rate of CD4 T cell depletion in the Korean population.

Suh *et al.* (2002, only abstract available)

Suh *et al*. (2002) investigated the effect of red ginseng powder on postoperative immunity and survival in patients with stage III gastric cancer. Flow cytometric analyses for peripheral T-lymphocyte subsets in patients during postoperative chemotherapy after a curative resection with D2 lymph node dissection showed that red ginseng powder restored CD4 levels to the initial preoperative values during postoperative chemotherapy. Depression of CD3 during postoperative chemotherapy was also inhibited. The study demonstrated a five-year disease free survival and overall survival rate that was significantly higher in patients taking the red ginseng powder during postoperative chemotherapy versus control. The authors stated that in spite of the limitation of a small number of patients (n=42), these findings suggest that red ginseng powder may help to improve postoperative survival in these patients. Additionally, red ginseng powder may have some immunomodulatory properties associated with CD3 and CD4 activity in patients with advanced gastric cancer during postoperative chemotherapy.

Tode *et al.* (1999)

The objective of the study was to investigate the effect of Korean red ginseng on psychological functions in postmenopausal patients with severe climacteric syndromes. ACTH, cortisol and DHEA-S in peripheral blood from 12 postmenopausal women with climacteric syndrome and 8 postmenopausal women without any climacteric syndrome were measured before and 30 days after treatment with daily oral administration of 6 g red ginseng. In postmenopausal women with climacteric syndrome such as fatigue, insomnia and depression, psychological tests using the Cornell Medical Index (CMI) and the State-Trait Anxiety Inventory (STAI) were performed before and 30 days after treatment. CMI score as well as anxiety state in STAI score in postmenopausal women with climacteric syndrome was significantly higher than that without climacteric syndrome, while DHEA-S levels in postmenopausal women with climacteric syndrome were about a half of those without climacteric syndrome. Treatment with daily oral administration of 6 g red ginseng for 30 days led to a decrease of CMI and STAI-scores within normal range. Even though the DHEA-S levels were not restored to the levels in postmenopausal women without climacteric syndrome, the cortisol/DHEA-S-ratio decreased significantly after treatment with red ginseng. The authors concluded that improvement of CMI and STAI scores, particularly fatigue, insomnia, and depression, by red ginseng seemed to be brought about in part by effects of red ginseng on stress-related hormones.

Dry extract (DER 3-7:1), extraction solvent ethanol 40% V/V, containing 4% ginsenosides (sum of Rb_1, Rb_2, Rc, Rd, Re, Rf, Rg_1, Rg_2) (G115)

This dry extract (often referred as special extract G115) is in medicinal use in the European Union since 1981. The extract has been tested in numerous clinical studies in different indications. In 2005 a review on G115 was published (Scaglione *et al.* 2005). Studies which were not included in the review are additionally briefly described in the following section.

<u>Scaglione *et al.* 2005 (Review on G115)</u>

Scaglione *et al*. reviewed the properties and usage of the standardized *Panax ginseng* C.A. Meyer extract G 115. In the clinical part of the review the authors focused on double-blind, placebo-controlled trials of scientific relevance. A number of non GCP conform studies that have been conducted in the 1980s and 1990s, especially the studies on endurance and vitality (Dörling 1980, Forgo *et al.* 1981a, Gross *et al.* 1995), psychoasthenia (Mulz *et al.* 1990, Rosenfeld 1989, Gianoli & Riebenfeld 1984), and on psychomotor functions (Forgo 1983, van Schepdael 1993, Forgo *et al.* 1981 b, Forgo & Kirchdorfer 1982, Forgo & Schimert 1985) is also mentioned. Almost all of the non GCP conform studies show positive outcomes, therefore, the authors state that further GCP conform studies are required to confirm these results. GCP-conform studies on the efficacy of G115 in menopause (Wiklund *et al.* 1999), cognitive functions (Kennedy *et al.* 2001, Kennedy *et al.* 2002), and immunology (Scaglione *et al.* 1996, Scaglione *et al.* 2001) are briefly reported:

Wiklund *et al.* (1999) conducted a double-blind placebo-controlled study on 384 symptomatic postmenopausal women, which were treated with either 100 mg G115 twice daily (n=193) or placebo (n=191) for 16 weeks to assess the effect of G 115 on quality of life and hormonal levels. No significant changes were found for the levels of the follicle-stimulating hormone and estradiol, ultrasound and vaginal cytology values in either group. The total psychological general well-being score (PGWB) did not show any significant difference between verum and placebo, although a significantly better effect was seen for G115 regarding depressed mood ($p<0.04$), general health ($p<0.03$) and well-being ($p<0.05$). G 115 had no effect on vasomotor symptoms but was superior to placebo in enhancing well-being and relieving somatic symptoms.

Kennedy *et al*. (2001) report a randomized, double-blind, placebo-controlled, balanced-crossover study with 20 participants receiving three different single doses of the relevant extract and an identical-looking placebo on separate occasions 7 days apart. The 400 mg dose was associated with improvements on “quality of memory”. In contrast to these improvements, both of the less active doses (200 mg and 600 mg) were associated with a significant decrement of the “speed of attention” factor at later testing times only. Subjective ratings of alertness were also reduced 6 h after the two lowest doses.

Kennedy *et al*. (2002) report on a study similar designed as the above mentioned study (Kennedy *et al.* 2001). The positive results with 400 mg G115 on “quality of memory” were confirmed. Furthermore, the efficacy of single doses of a standardized extract of *Ginkgo biloba*, G115 and their combination against placebo was investigated resulting in a positive outcome.

Scaglione *et al*. (1996) report on the investigation of efficacy and safety of G 115 for potentiating vaccination against the common cold and/or influenza syndrome in a randomized, double blind, placebo-controlled, parallel-group multicenter study. 227 volunteers were treated for 12 weeks with either G115 100 mg (n=114) or placebo (n=113) twice daily. After 4 weeks of treatment they were vaccinated with an anti-influenza vaccine. The frequency of influenza or common cold between weeks 4 and 12 in the G 115 group was significantly lower ($p<0.001$) compared to the placebo group. Antibody titres and NK activity levels after 8 weeks were significantly higher in the G115 group ($p<0.0001$) compared to placebo.

In an open pilot study (Scaglione *et al.* 2001) the effects of G115 in reducing the bacterial count in the bronchial system of patients undergoing an acute attack of chronic bronchitis were investigated. 75 patients experiencing acute attacks of chronic bronchitis were included in the trial. All were treated with amoxicillin and clavulanic acid twice daily. They were then further randomly divided into two groups, one (n=37) receiving only the antibiotic treatment, the other (n=38) also G115 100 mg twice daily. The duration of treatment was 9 days on average. Of the 75 patients included in the trial 44 were evaluable. Significant group and day effects were found after analysis of the evolution of bacterial count. In the group receiving G115 the bacterial clearance was significantly higher than in the group receiving the antibacterial alone.

Scaglione *et al*. (2005) concluded that in most indications results were contradictory but more recent placebo-controlled double-blind studies have shown that G115 might modify parameters related to cognitive and psychological function as well as immunological function in a positive way.

<u>Further relevant clinical studies on G115:</u>

Cognition and cerebrovascular function:

<u>Reay *et al.* (2010)</u>

Reay *et al*. (2010) investigated the effects of G115 on subjective mood and aspects of working memory processes following a single dose and following seven days ingestion in healthy volunteers in a placebo-controlled, double-blind, randomised crossover study. Thirty volunteers (mean age 23 years) received each treatment (G 115 200 mg, 400 mg, placebo) for 8 days, in a counter balanced order, with a 6-day wash-out period. Testing was performed on days 1 and 8 of each treatment period, at pre-dose, 1, 2.5, and 4 h post-dose. Dose related treatment effects ($p<0.05$) were observed. 200 mg slowed a fall in mood at 2.5 and 4 h on day 1 and 1 and 4 h on day 8 but slowed responding on a mental arithmetic test across day 1 and at 1 and 2.5 h on day 8. The 400 mg dose also improved calmness (restricted 2.5 and 4 h on day 1) and improved mental arithmetic across days 1 and 8. The study revealed that 7 consecutive days of ginseng ingestion had no effect on mood or cognitive performance. However, results showed that single doses of G 115 could modulate working memory performance and improve participants’ subjective self-reports on calmness. Given that ginseng is typically ingested repeatedly the authors concluded that further research is needed to investigate the behavioural effects following longer periods of ginseng ingestion.

<u>Reay *et al.* (2008)</u>

Reay *et al*. (2008) investigated the behavioural and mood effects of G115 in a 20 week double-blind, placebo-controlled, cross-over study. 25 healthy volunteers (mean age 35 years) received each treatment (placebo, 200 mg G115) for 57 days in total with a wash-out period of 27 days between treatments. Behaviour was assessed on days 1, day 29 and day 57 of each treatment period. The behavioural assessment was conducted at pre-dose and 3 h post-dose on each testing day and comprised the CDR (Cognitive Drug Research) computerised assessment battery and a collection of verbal and non-verbal working memory tasks. Subjective quality of life and mood were also measured. Results revealed improvements in working memory following a single acute dose of G115 whereas following chronic dosing results revealed both, improvement and decrement in aspects of cognition and mood.

Sünram-Lea *et al.* (2005)

Sünram-Lea *et al*. (2005) investigated the effect of acute administration of 400 mg of G115 on mood and cognitive performance in a double-blind, placebo-controlled, balanced, cross-over design. Thirty healthy young adult volunteers (mean age 20 years) received 400 mg of G115 and a placebo in a counterbalanced order with a 7-day wash-out period between treatments. Following baseline evaluation of cognitive performance and mood measures, participants' cognitive performance and mood was assessed again 90 minutes after drug ingestion. Ginseng improved speed of attention, indicating a beneficial effect on participants' ability to allocate attentional processes to a particular task. No significant effect was observed on any other aspect of cognitive performance and on self-reported mood measures.

Sünram-Lea *et al.* (2003)

Assessor's comment:

An abstract of a poster or lecture is available, full data was published in 2005 (Sünram-Lea et al. 2005)

D'Angelo *et al.* (1986)

D'Angelo *et al*. (1986) investigated the effect of G 115 on psychomotor performance in a randomised, double-blind, placebo-controlled study. Thirty-two male volunteers (mean age 22 years) were treated with either 200 mg of G115 daily or placebo for 12 weeks. The psychomotor performance was assessed using a variety of test systems (tapping test, simple reaction time, choice reaction time, cancellation test, digit symbol substitution test, mental arithmetic test, logical deduction). A favourable effect of G115 relative to baseline performance was observed in attention (cancellation test), processing (mental arithmetic, logical deduction), integrated sensory-motor function (choice reaction time) and auditory reaction time. However, end performance of the G115 group was superior statistically to the placebo group only in mental arithmetic.

Quiroga (1982)

Quiroga (1982) investigated G 115 in a comparative double-blind study on patients with different degrees of cerebrovascular deficits classified into three groups. Forty-five patients (aged between 40 and 76 years) received either placebo, 200 mg G 115 or 3 mg Hydergin per day during 90 days. Rheoencephalographic controls were conducted prior to the treatment as well as after 30, 60, and 90 days of treatment. The G115 group showed improvement quotients of 30% to 45% with respect to the pre-treatment values. Hydergin led to improvement quotients of more than 50% whereas in the placebo group no improvement was observed.

Chronic respiratory diseases:

<u>Xue *et al.* (2011)</u>

Xue *et al*. (2011) described the study protocol of a randomised, multi-centre, double-blind, placebo controlled two-armed parallel clinical trial on the therapeutic value and the safety profile of G115 in the symptomatic relief of moderate COPD with a focus on quality of life improvements. Two trial sites in Melbourne (Australia) would proportionately randomize a total of 168 participants to receive either 100 mg ginseng extract or placebo twice daily for 24 weeks. The primary outcomes would be based on three validated QoL questionnaires, St. Georges Respiratory Questionnaire (SGRQ), Short Form Health Survey (SF-36) and the COPD Assessment Test (CAT). Secondary outcomes would be based on lung function testing, relief medication usage and exacerbation frequency and severity. Safety endpoints would include blood tests and adverse event reporting. Results were expected to be published in late 2012 or early 2013.

Assessor's comment:

A check of the Australia and New Zealand Clinical Trials Register (ANZCTR, http://www.anzctr.org.au/) on 10.1.2014 for the respective registration number (ACTRN12610000768099) revealed that the study is still in the recruitment phase.

<u>Gross *et al.* (2002)</u>

Gross *et al*. (2002) investigated one hundred patients with COPD. They were randomly assigned by a random number table into the experimental and placebo-control groups. Inclusion criteria included COPD of moderate severity, defined as forced expiratory volume at the first second of expiration (FEV 1.0) 50-65% of predicted, clinical stability in the six months preceding the study and ability to exercise without hemodynamic instability. Study participants received 100 mg ginseng extract G115 twice daily for three months. Placebo capsules that resembled the G115 capsules were administered twice daily to the control participants for three months. Neither patients nor the investigators were aware of group assignment. Current medical treatment was continued throughout the study period. Effects on Pulmonary Function Tests (PFTs), Maximum Voluntary Ventilation (MVV), Maximum Inspiratory Pressure (MIP), and Maximal Oxygen Consumption (VO_2max) were evaluated. Overall, 92 patients have completed the study. Patients drop out was related to unwilling to continue further testing but not related to side effects. In the placebo group no change was observed in any of the parameters at any time point. In the experimental group all parameters began to improve after two weeks of treatment except for FEV 1.0/FVC ratio, which did not change throughout the study period. The treatment has not been associated with any adverse events. The authors concluded that a 200 mg/day G115 treatment induced an increase in pulmonary function tests, respiratory endurance and strength and maximum oxygen consumption in patients with moderately severe chronic obstructive pulmonary disease.

Quality of life and physiological parameters:

<u>Cardinal & Engels (2001)</u>

Cardinal & Engels (2001) investigated the effects of G115 on psychological well-being in healthy young adults in a prospective, randomised, double-blind, placebo-controlled clinical trial. 83 participants (mean age 26 years) received placebo, 200 mg or 400 mg ginseng extract per day for 8 weeks. The main outcome measures were positive affect, negative effect, and total mood disturbance. Measures were obtained before starting the ginseng-supplementation and between 56 to 60 days of supplementation by application of the PANAS (Positive Affect-Negative Affect Scale) and the POMS (Profile of Mood States) inventory. Results showed that Ginseng supplementation had no effect on positive affect, negative affect, and total mood disturbance in healthy young adults.

Engels *et al.* (2001, only abstract available)

Engels *et al*. (2001) investigated the effects of long-term ginseng supplementation on short supramaximal exercise performance and short-term recovery. In a randomised, double-blind, placebo-controlled study 24 healthy, active women received either 400 mg G115 per day or placebo in addition to their normal diet for 8 weeks. Before and after the trial period, each subject performed an all-out-effort, 30-second leg cycle ergometry test followed by a controlled recovery under constant laboratory conditions. Nineteen subjects completed the study. Analysis of variance using pre-test to post-test change scores revealed no significant difference between the ginseng and placebo study groups for peak anaerobic power output, mean anaerobic power output, rate of fatigue, and immediate post-exercise recovery heart rates ($p>0.05$). In conclusion, the data indicated that prolonged supplementation with G 115 has no ergogenic benefits during and in the recovery from short, supramaximal exercise.

Engels & Wirth (1997)

Engels & Wirth (1997) investigated the effects of chronic supplementation with G115 on physiologic and psychological responses during graded maximal aerobic exercise in a randomised double-blind, placebo controlled trial. Thirty-six healthy men received placebo, 200 or 400 mg per day of the standardized *Panax ginseng* extract G115 in addition to a normal diet for 8 weeks. Each study participant was evaluated under controlled laboratory conditions before and after the G 115 supplementation. The results revealed that there was no effect on the ergogenic parameters oxygen consumption, respiratory exchange ratio, minute ventilation, blood lactic acid concentration, heart rate, and perceived exertion during graded maximal aerobic exercise.

Blood glucose regulation:

Reay *et al.* (2009)

Twenty-three volunteers completed a randomized, placebo-controlled, cross-over study which investigated the effects of G115 on blood glucose regulation. Each participant received two capsules daily containing either 100 mg G115 or placebo for 57 days. Before cross-over participants were subjected to a 27-days washout period. Blood samples were collected according to a protocol and analysed for HbA_{1c}, fasting plasma insulin and fasting plasma glucose. There were no significant effects on any of the three parameters on day 1, 27, and 59 of the study. The authors concluded that chronic ingestion of G115 had no impact on indices of glucose regulation in non-diabetic humans.

Reay *et al.* 2006a

Reay *et al.* (2006a) investigated the effects of G115 single doses on blood glucose levels and cognitive performance in a double-blind, placebo-controlled, balances-crossover study including 27 healthy young adults. Each of the participants had to complete a 10 minute “cognitive demand” test battery. Then they received two capsules, each containing either 100 mg G115 or placebo and 30 minutes later a drink containing glucose or placebo. Further minutes later they completed the “cognitive demand” battery six times in immediate succession. Depending on the treatment group the combination of capsules/drink corresponded to a dose of: 0 mg G115/0 mg glucose (placebo); 200 mg G115/0 mg glucose (ginseng), 0 mg G115/25 g glucose (glucose) or 200 mg G115/25 g glucose (ginseng/glucose combination). Blood glucose levels were measured prior to the treatment, and before and after the post-dose completions of the battery. The results showed that both, G115 and glucose enhanced performance of a mental arithmetic test and ameliorated the increase in subjective feelings of mental fatigue experienced by participants during the later stages of the sustained, cognitively demanding task performance. There was no evidence of a synergistic relationship between G115 and exogenous glucose ingestion on any cognitive outcome measure. G115 caused a reduction in blood glucose levels 1 hour following consumption when ingested without glucose. The authors concluded that G115 might possess glucoregulatory properties and could enhance cognitive performance.

Reay *et al.* (2006b)

In two separate acute placebo-controlled, double blind, crossover studies in healthy young adults the effects of G115 on blood glucose levels were investigated. In study 1, thirty participants received three treatments: placebo, 200 mg G115, and 400 mg G115. In study 2 twenty-seven participants received four treatments: placebo (0 mg G115 and 30 mg saccharin), ginseng (200 mg G115 and 30 mg saccharin), placebo-glucose (0 mg G115 and 25 g oral glucose), and ginseng-glucose (200 mg G115 and 25 g oral glucose) Blood glucose levels were measured at baseline after an overnight fast and then 60, 90, and 120 min post dose. Both studies demonstrated that G115 alone significantly lowers fasting blood glucose levels. Conversely, in study 2, there was a significant drink-G115 interaction suggesting that in presence of elevated blood glucose levels administration of G115 leads to a further increase of blood glucose. The authors suggested that diabetes patients should exercise caution in the use of ginseng products due to its gluco-modulating properties.

Reay *et al.* (2005)

In a double-blind, placebo-controlled, balanced crossover study including 30 healthy young adults the effects of G115 on cognitive performance and blood glucose levels were investigated. A 10 minutes test battery at baseline and 60 min after treatment with either placebo, 200 mg G115 or 400 mg G115 had to be completed by the participants. Blood glucose was measured prior to the treatment and before, during, and after the post-dose completions of the battery. Both, the 200 mg and the 400 mg treatments led to significant reductions in blood glucose levels at all three post-treatment measurements. The most notable behavioral effects were associated with 200 mg of G115 suggesting that G115 can improve performance and subjective feelings of mental fatigue during sustained mental activity. The authors stated that this effect might be related to the acute glucoregulatory properties of the extract. However, the mechanism of action requires further investigation.

Systematic reviews on general safety and efficacy of *Panax ginseng*:

Lee & Son (2011): Systematic Review of Randomized Controlled Trials Evaluating the Efficacy and Safety of Ginseng

This systematic review aimed to evaluate the available evidence from randomized clinical trials of the clinical efficacy and safety of ginseng up to March 2009. A total of 57 randomized clinical trials evaluating the clinical effects or safety of the use of ginseng monopreparations (*Panax ginseng* or *Panax quinquefolius*) were considered for inclusion. The main indications included glucose metabolism (12 trials), physical performance (9 trials), psychomotor function (8 trials), sexual function (7 trials), cardiac function (6 trials), pulmonary disease (6 trials), and cerebrovascular function (9). For details regarding the clinical trials see **Table 1**.

Glucose metabolism:

Twelve studies investigated the effects of ginseng on glucose metabolism [Vuksan *et al.* (2008), Reay *et al.* (2006a, b), Sievenpiper *et al.* (2006), Reay *et al.* (2005), Sievenpiper *et al.* (2004), Sievenpiper *et al.* (2003a), Sievenpiper *et al.* (2003b; *Panax quinquefolius*), Vuksan *et al.* (2001; *Panax quinquefolius*), Vuksan *et al.* (2000a, b, c; *Panax quinquefolius*)]. The methodology of 11 of these studies was good in opinion of the authors, reaching three or more points on the Jadad scale. Of the 11 high-quality trials, eight had positive results, two had negative results and one yielded variable results. The authors concluded that there was strong evidence to suggest that ginseng shows positive effects on glucose metabolism.

Physical performance:

The efficacy of ginseng on physical performance was evaluated in nine trials including healthy volunteers and athletes as well as sedentary men [Kulapuntana *et al.* (2007), Engels *et al.* (2003), Yoon *et al.* (2008, only abstract available), Hsu *et al.* (2005; *Panax quinquefolius*), Engels *et al.* (2001), Allen *et al.* (1998), Engels & Wirth (1997), Morris *et al.* (1996; *Panax quinquefolius*), Engels *et al.* (1996)]. The duration of ginseng use lasted from one to eight weeks. The methodological quality of eight trials was good according to the authors, scoring more than three points on the Jadad scale. All of the studies yielded negative results; therefore ginseng was not shown to enhance physical performance with strong evidence according to the authors.

Psychomotor function:

Eight trials with good methodology (Jadad score more than 3 points in 5 of the eight trials) evaluated the efficacy of ginseng on psychomotor function using white or red ginseng [Lee ST *et al.* (2008, only abstract available), Heo *et al.* (2008), Sünram-Lea *et al.* (2005), Scholey & Kennedy (2002), Kennedy *et al.* (2002; combination with ginkgo), Kennedy *et al.* 2001, Cardinal & Engels (2001), Ziemba *et al.* 1999). The studies yielded six positive and two negative findings. The authors concluded that there was a strong evidence of efficacy in the indication psychomotor function.

Sexual function:

Seven RCTs investigated the effects of ginseng on erectile dysfunction [De Andrade *et al.* (2007), Choi *et al.* (2003, only abstract available), Hong *et al.* (2002, only abstract available), Choi & Choi (2001 ,no abstract available), Kim & Paick (1999, only abstract available), Choi *et al.* (1999, only abstract available), Choi *et al.* (1995, only abstract available)]. The methodology of six of these studies was poor, scoring less than three points on the Jadad scale. One high quality trial revealed a negative result and the six low quality studies had positive results. Lee & Son (2011) concluded that there was moderate evidence that ginseng might have positive effects in erectile dysfunction.

Cardiac function:

Six studies investigated the effects of ginseng on cardiac function or disease [Stavro *et al.* (2005; *P. quinquefolius*), Stavro *et al.* (2006; *Panax quinquefolius*), Caron *et al.* (2002), Ding *et al.* (1995, only abstract available), Zhao (1990, only abstract available), Zhan *et al.* (1994, only abstract available)]. Three of the studies were of high quality, with a Jadad score of three or more points. Four of the studies had positive results and two had negative findings, indicating moderate evidence in the authors' opinion.

Pulmonary disease:

Six studies assessed the effects or safety of ginseng on pulmonary diseases [Vohra *et al.* (2008; *Panax quinquefolius*), McElhaney *et al.* (2006; *Panax quinquefolius*), Predy *et al.* (2005; *Panax quinquefolius*), McElhaney *et al.* (2004; *Panax quinquefolius*), Gross *et al.* (2002), Scaglione *et al.* (2001)]. The studies were of high quality, scoring three or more points on the Jadad scale, and all five yielded positive findings. Therefore, the authors concluded that there was strong evidence of the efficacy of ginseng in approving pulmonary function and prevention of respiratory diseases.

Cerebrovascular function:

Two studies investigated the effects of ginseng on cerebrovascular function (Jeong *et al.* 2006, only abstract available; Kennedy *et al.* (2003; combination with ginkgo). One study was of high quality scoring four points, the other one was of low quality scoring only two points on Jadad scale. Both studies showed positive results indicating moderate evidence according to the authors.

<u>Safety:</u>

Thirty of the 57 trials reported the presence or absence of adverse events: 16 reported some side effects, whereas 14 found no side effects during the trials. The 27 other trials did not address the topic. Some side effects were species related. *Panax ginseng* was associated with gastrointestinal problems ranging from stomach discomfort and nausea to vomiting and diarrhoea. Red ginseng was associated with gastric upset, with one case of hypoglycaemia, and *Panax quinquefolius* was associated with insomnia, headache, chest discomfort, and diarrhoea plus type 2 diabetes mellitus.

Table 1

Reference	Jadad score	Design	Participants and sample size	Intervention/control (dosage)	Primary endpoint	Main results	Frequency of adverse events
Glucose metabolism							
Vuksan *et al.* (2008)	5	Crossover	39 patients with type 2 diabetes	Red ginseng (6g)/placebo for 12 weeks	Efficacy and safety of use for type 2 diabetes	Improved plasma glucose and insulin regulation	One case of hypoglycemia
Reay *et al.* (2006b)	2	Crossover (single dose study)	57 healthy subjects	*P. ginseng* extract "G115" (0.2 or 0.4 g)/placebo	Glucoregulatory effects of single ginseng dose	Poor glucoregulation	None
Sievenpiper *et al.* (2006)	4	Crossover (single dose study)	19 healthy subjects	Red ginseng (2, 4, or 6 g)/placebo	Glucoregulatory effects: preparation and dose-finding study	Good glucoregulation using 2 g rootlet	None
Reay *et al.* (2006a)	4	Crossover (single dose study)	27 healthy subjects	*P. ginseng* extract "G115" (0.2 g)/placebo	Effects on blood glucose level and cognitive performance	Improved glucose level and enhanced cognitive performance	Not described
Reay *et al.* (2005)	5	Crossover (single dose study)	30 healthy subjects	*P. ginseng* extract "G115" (0.2 g)/placebo	Glucoregulation and cognition improvement	Glood glucoregulation and cognitive function	Not described
Sievenpiper *et al.* (2004)	3	Crossover (single dose study)	12 healthy subjects	*P. ginseng* extract (3g)/placebo	Glucoregulatory effects of multiple types of ginseng	Variable effects according to ginsenoside profile	Not described
Sievenpiper *et al.* (2003a)	3	Crossover (single dose)	22 healthy subjects	*P. ginseng* (1, 2, 3, 6, or 9 g)/placebo	Glucoregulatory effects - acute dose escalation study	Null and opposing effects	Not described
Sievenpiper *et al.* (2003b)	3	Crossover (single dose)	12 healthy subjects	*P. quinquefolius* (6 g)/placebo	Glucoregulatory effects of different batches	Poor glucoregulation	Not described
Vuksan *et al.* (2001)	3	Crossover (single dose)	12 healthy subjects	*P. quinquefolius* (1, 2, or 3 g)/placebo	Time and dosing effect on postprandial glycemia	Good glucoregulation in a time-dependent manner	None
Vuksan *et al.* (2000a)	3	Crossover (single dose)	10 healthy subjects	*P. quinquefolius* (3, 6, or 9 g)/placebo	Glucoregulatory effects on healthy subjects	Good glucoregulation (irrespective of time and dose)	None
Vuksan *et al.* (2000b)	3	Crossover (single dose)	10 patients with type 2 diabetes	*P. quinquefolius* (3, 6, or 9 g)/placebo	Glucoregulatory effects on patients with diabetes	Good glucoregulation (irrespective of time and dose)	None
Vuksan *et al.* (2000c)	3	Crossover (single dose)	10 healthy subects/9 patients with diabetes	*P. quinquefolius* (3 g)/placebo	Glucoregulatory effects on different groups	Good glucoregulation of both participant groups	One case of mild insomnia
Physical performance							
Yoon *et al.* (2008)	3	Parallel (3 arms)	30 healthy subjects	Red ginseng (3g)/placebo for 8	Effect on aerobic, anaerobic performance,	No significant effects	Not described

				weeks	central and peripheral fatigue		
Kulaputana *et al.* (2007)	4	Parallel (2 arms)	60 healthy sailors	*P. ginseng* (3g)/placebo for 8 weeks	Effects on exercise performance with lactate threshold	No significant effects	Not described
Hsu *et al.* (2005)	2	Crossover	13 healthy men	*P. quinquefolius* (1.6 g)/placebo for 4 weeks	Effects on creatine kinase and lactate during endurance exercise	Decreased creatine kinase, no change in other parameters	Not described
Engels *et al.* (2003)	4	Parallel (2 arms)	38 healthy subjects	*P. ginseng* extract "G115" (0.4 g)/placebo for 8 weeks	Effects on heart rate recovery, secretory IgA after exercise	No significant effects	Not described
Engels *et al.* (2001)	4	Parallel (2 arms)	24 healthy women	*P. ginseng* extract "G115" (0.4 g)/placebo for 8 weeks	Effects on recovery from short, supramaximal exercise	No significant effects	One case of stomach discomfort
Allen *et al.* (1998)	4	Parallel (2 arms)	28 healthy subjects	*P. ginseng* extract (0.2 g) for 3 weeks	Effects on peak aerobic exercise performance	No significant effects	Two cases of mild diarrhea
Engels & Wirth (1997)	4	Parallel (3 arms)	36 healthy men	*P. ginseng* extract "G115" (0.2 or 0.4 g)/placebo for 8 weeks	Effects during graded maximal aerobic exercise	No significant effects	Three cases of diarrhea in high-dosage group
Morris *et al.* (1996)	4	Parallel (3 arms)	8 healthy subjects	*P. quinquefolius* extract (8 or 16 mg/kg)/placebo for 1 week	Effects on physical response to intense exercise	No significant effects	Not described
Engels *et al.* (1996)	3	Parallel (2 arms)	19 healthy female subjects	*P. ginseng* extract (0.2 g)/placebo for 8 weeks	Effects on work performance and energy metabolism	No significant effects	Not described
Psychomotor function							
Lee ST *et al.* (2008)	2	Parallel (2 arms)	97 patients with Alzheimer's disease (AD)	*P. ginseng* (4.5 g)/placebo for 12 weeks	Effects on cognitive performance of AD patients	Significantly effective in the cognitive performance of AD patients	Two cases of heat sense, one case of dizziness, nausea, anorexia, diarrhea, and headache
Heo *et al.* (2008)	2	Parallel (3 arms)	61 patients with AD	Red ginseng (4.5 or 9 g)/placebo for 12 weeks	Efficacy of the treatment of AD	High dose group showed significant improvement in Alzheimer's Disease Assessment Scale and Clinical Dementia Scale	Two cases of fever (low dose), two cases of nausea (high dose)
Sünram-Lea *et al.* (2005)	5	Crossover (single dose)	30 healthy subjects	*P. ginseng* extract "G115" (0.4 g)/placebo	Effects on cognitive performance and mood	No significant effect, except for "speed of attention"	Not described
Scholey & Kennedy (2002)	4	Crossover (single dose)	20 healthy subjects	*P. ginseng* extract "G115" (0, 0.2, 0.4, or 0.6 g)/placebo	Dose-dependent effect on cognitive function	Improved accuracy and time of responses	Not described

Kennedy *et al.* (2002)	4	Crossover (single dose)	20 healthy subjects	*P. ginseng* extract “G115” (0.4 g)/placebo	Effects on modulation of cognition and mood	Positively affected cognitive performance	Not described
Kennedy *et al.* (2001)	3	Crossover (single dose)	20 healthy subjects	*P. ginseng* extract “G115” (0.2, 0.4 or 0.6 g)/placebo	Effects on cognitive performance	Affected cognition in time-/dose-dependent manner	Not described
Cardinal & Engels (2001)	4	Parallel (3 arms)	83 healthy subjects	*P. ginseng* extract “G115” (0.2 or 0.4 g)/placebo for 8 weeks	Effects on mood	No significant effect	Not described
Ziemba *et al.* (1999)	2	Parallel (2 arms)	15 healthy subjects	*P. ginseng* extract (0.35 g)/placebo for 3 weeks	Effects on psychomotor performance	Improved psychomotor performance	Not described
Sexual function							
De Andrade *et al.* (2007)	2	Parallel (2 arms)	60 subjects with erectile dysfunction (ED)	Red ginseng (3g)/placebo for 12 weeks	Effects on ED	Significantly improved International Index of Erectile Function-5 (IIEF-5) score	None
Choi *et al.* (2003)	2	Parallel (2 arms)	30 patients with ED	Red ginseng (1.8 g)/placebo for 4 weeks	Effect on penile blood flow of patients with ED	Significantly improved penile blood flow	One case of gastric discomfort
Hong *et al.* (2002)	2	Crossover	45 subjects with ED	Red ginseng (2.7 g)/placebo for 8 weeks	Effects on ED	Significantly improved IIEF-5 score and penile tip rigidity	Not described
Choi & Choi (2001)	1	Parallel (2 arms)	50 patients with ED	Red ginseng (1.8 g)/placebo for 8 weeks	Effects on ED	Significantly effective for ED	One case of gastric discomfort
Kim & Paick (1999)	4	Parallel (2 arms)	26 patients with mild impotence	Red ginseng (2.7 g)/placebo for 12 weeks	Effect on vasculogenic impotence	No significant effect except for sexual satisfaction score	Not described
Choi *et al.* (1999)	2	Parallel (2 arms)	50 patients with ED	Red ginseng (1.8 g)/placebo for 12 weeks	Effects on ED	Significantly effective for ED	Two cases of constipation, two cases of gastric upset
Choi *et al.* (1995)	1	Parallel (3 arms)	90 patients with ED	Red ginseng (1.8 g)/placebo for 12 weeks	Effects on ED	Significantly effective for ED	Not described
Cardiac function							
Stavro *et al.* (2006)	3	Crossover	52 hypertensive subjects	*P. quinquefolius* (3 g)/placebo for 12 weeks	Effects on hypertension	No significant effect	One case of diarrhea and one of headache
Stavro *et al.* (2005)	3	Crossover	16 hypertensive subjects	*P. quinquefolius* (3 g)/placebo for 12 weeks	Effects on hypertension	No significant effect	None
Caron *et al.* (2002)	3	Parallel (2 arms)	30 healthy subjects	*P. ginseng* exctract “G115” (0.2	Effects on electrocardiograph	Increased QTc interval, decreased	One case of nausea and vomiting

				g)/placebo for 4 weeks		diastolic blood pressure	
Ding *et al.* (1995)	2	Parallel (3 arms)	45 patients with class IV cardiac function	Red ginseng (6g) for 15 days	Effects on congestive heart failure	Showed significant effect as safe adjuvant	None
Zhan *et al.* (1994)	2	Parallel (3 arms)	30 patients with mitral-valve disease	*P. ginseng* saponins (0.6 or 1.2 mg/kg)/placebo for 10 days	Effect on myocardial ischemia reperfusion injury (IRI)	Showed protective effect against IRI	Not described
Zhao (1990)	2	Parallel (2 arms)	481 patients with coronary heart disease (CHD)	*P. ginseng* saponins (0.15 g)/placebo for 8 weeks	Effect on aging and angina pectoris due to CHD	Alleviated aging symptoms and angina pectoris	None
Vohra *et al.* (2008)	5	Parallel (3 arms)	75 children with upper respiratory tract infection (URTI)	*P. quinquefolius* extract (9-26 or 4.5-13 mg/kg) for 3 days	Safety and tolerability in the treatment of pediatric URTI (phase 2 study)	Standard doses (9-26 mg/kg) are appropriate for phase 3	No serious adverse events
McElhaney *et al.* (2006)	5	Parallel (2 arms)	43 elderly subjects	*P. quinquefolius* extract "COLD-fX" (0.4 g)/placebo for 16 weeks	Effects on prevention of acute respiratory illness (ARI)	Significantly reduced the risk and duration of ARI	Nonspecific adverse effects
Predy *et al.* (2005)	5	Parallel (2 arms)	323 subjects with history of colds	*P. quinquefolius* extract (0.4 g)/placebo for 16 weeks	Effects on prevention of common colds	Significantly reduced the risk of colds	Two cases of type 2 diabetes mellitus
McElhaney *et al.* (2004)	4	Parallel (2 arms)	198 elderly subjects	*P. quinquefolius* extract "CVT-E002" (0.4 g)/placebo for 8-12 weeks	Effects on prevention of ARI	Effective at preventing ARI	None
Gross *et al.* (2002)	4	Parallel (2 arms)	100 subjects with COPD	*P. ginseng* extract "G115" (0.2 g)/placebo for 12 weeks	Effect on pulmonary function in patients with COPD	Improved pulmonary function in patients with COPD	None
Scaglione *et al.* (2001)	2	Parallel (2 arms)	75 patients with chronic bronchitis	*P. ginseng* extract "G115" (0.2 g)/placebo for 9 days	Effects on chronic bronchitis	Significantly effective in bacterial clearance	Not described
Cerebrovascular function							
Jeong *et al.* (2006)	2	Crossover (single dose)	10 healthy men	*P. ginseng*/red ginseng/fermented red ginseng extract (0.2 g)	Effects on cerebral blood flow and cerebrovascular reactivity	Enhanced cerebrovascular reactivity and increased cerebral blood flow	None
Kennedy *et al.* (2003)	4	Crossover (single dose)	15 healthy subjects	*P. ginseng* extract "G115" (0.2 g)	Electroencephalograph effects of a single dose of ginseng	Directly modulated cerebroelectrical activity	Not described

Assessor's comment:

The systematic review by Lee & Son (2011) has to be interpreted with caution because of the heterogeneity and in most cases low methodological quality of the included studies. The authors evaluated preparations of Panax ginseng as well as preparations of Panax quinquefolius. Furthermore, it is neither differentiated between red and white ginseng nor between comminuted or powdered herbal substance and extracts.

For the evaluation of effects on glucose metabolism single dose studies were evaluated together with studies that investigated the long term use of ginseng preparations. Therefore, firm overall conclusions on the efficacy of Panax ginseng preparations on glucose metabolism cannot be drawn (see also the systematic review by Buettner et al. 2006). The effects on physical performance of red ginseng, white ginseng (powdered roots), and the ginseng extract G115 were investigated in several clinical studies with all of them showing negative results. The studies of high methodological quality which evaluated the effects of G115 on psychomotor function showed an improvement in some aspects. However, due to the small number of participants and the heterogeneity of test systems an overall conclusion on the evidence cannot be drawn (see also the systematic review by Geng et al. 2010). The clinical studies investigating the effects of red ginseng powder on erectile dysfunction were all of low methodological quality except one, which showed a negative outcome. Therefore, the evidence of red ginseng in this indication is doubtful (see also the systematic review by Jang et al. 2008). Studies on the investigation of "ginseng" effects on cardiac function are very heterogeneous (including the powdered roots of Panax quinquefolius as well as Panax ginseng, extracts, and ginseng saponins) and inconclusive, showing only minor influence on blood pressure and myocardial function (see also the systematic review by Buettner et al. 2006). In several studies the effects of "ginseng" preparations on pulmonary function and in the prevention of pulmonary diseases were investigated, but in most cases Panax quinquefolius was the source for preparations. Only two studies evaluated the Panax ginseng extract G115 showing positive effects on some parameters of pulmonary function in COPD patients (see also systematic review by Krebs Seida et al. 2011) and accelerating the bacterial clearance in patients suffering from chronical bronchitis. Only two studies were included in the evaluation of "ginseng" effects on cerebrovascular function. One study was of good methodological quality investigating the ginseng extract G115 but included only 15 participants, the other one was of low methodological quality and investigated various Panax ginseng preparations including only 10 participants. Therefore, strong evidence of a positive effect cannot be deduced from these studies.

To conclude, the systematic review by Lee & Son (2011) is of limited value for the assessment of evidence of efficacy of Panax ginseng preparations in the above mentioned indications because the data are too heterogeneous.

Vogler *et al.* (1999): The Efficacy of ginseng. A systematic review of randomised controlled trials

This systematic review provides an evaluation of evidence for or against the efficacy of ginseng root extract. Randomised, placebo-controlled trials of ginseng root extract for any indication until September 1998 have been considered. A total of 16 studies met the inclusion criteria. These trials assessed the effects of "ginseng root extracts" (including also *Panax quinquefolius* und *Eleutherococcus senticosus*) on physical performance, psychomotor performance and cognitive function, and immunomodulation.

<u>Physical performance:</u>

Seven trials investigated the effects of ginseng root extract on physical performance in young, active volunteers during submaximal and maximal exercises on cycle ergometers. The studies published by Forgo (1983), Forgo & Schimert (1985), and Cherdrungsi & Rungroeng (1995) revealed a significant decrease in heart rate and an increase in maximal oxygen uptake compared with placebo. Other studies on *Panax ginseng* (Engels *et al.* 1996, Engels & Wirth 1997), *Panax quinquefolius* (Morris *et al.* 1996) and *Eleutherococcus senticosus* (Dowling *et al.* 1996) found no improvement of physical performance. For details concerning clinical trials see **Table 2**.

Psychomotor performance and cognitive function:

Five studies investigated the effects of ginseng on psychological functions. Two of the studies on young healthy volunteers using *Panax ginseng* extract G115 (D'Angelo *et al.* 1986, Sörensen & Sonne 1996) reported significant improvements in mental arithmetic and abstraction tests, the third one (Smith *et al.* 1995, original article not available) revealed no improvement. In a further study on elderly people (Garcia 1988, original article not available) *Panax ginseng* extract was reported to be inferior compared to control (Vit B12 in combination with neurotrophic amino acids). However, the association test and inverted counting test showed significant improvement compared with baseline in the ginseng treated group. Moreover, two studies (Engels *et al.* 1996, Engels & Wirth 1997) investigated whether ginseng may alter psychological functions and improve tolerability to exercise-induced stress. The results suggested no significant effects on the ratings of perceived exertion during cycle ergometer tests (see also results on physical performance). For details concerning clinical trials see **Table 2**.

Immunomodulation:

Two studies assessed the effects of ginseng extracts on the immune system in healthy volunteers (Scaglione *et al.* 1990, Srisurapanon *et al.* 1997, only abstract available). Results are contradictory; one study reported a significant increase of the total number of T-Lymphocytes and of the activity of leucocytes compared with baseline after the ingestion of standardised *Panax ginseng* extract, whereas the other one found no effects on total and differential leucocyte counts and lymphocyte subpopulations. For details concerning the clinical trials see **Table 2**.

Blood glucose level: In one study (Sotaniemi *et al.* 1995) patients with newly diagnosed type 2 diabetes mellitus, who received either 100 mg or 200 mg ginseng daily, were assessed. At the end of an 8-week treatment period, psychophysical performance, mood and vigour were significantly improved compared with baseline in both ginseng groups. HbA_{1c} was significantly reduced in patients who received 200 mg ginseng, while a reduction of fasting blood glucose level was observed in both ginseng groups compared with baseline.

Table 2

Reference	Jadad score	Design	Participants and sample size (ginseng/control) age in years	Intervention/control (dosage)	Primary endpoint	Main results	Frequency of adverse events
Physical performance							
Forgo (1983)	3	Placebo controlled, 3 parallel groups	30 Healthy sportsmen 10/10/10 (range 18-31)	G 115 (100 mg twice daily)/G 115 + Vitamin E (100 mg, 200 mg respectively twice daily)/placebo for 9 weeks	Change of aerobic capacity, serum lactate, heart rate, hormone levels during ergometer exercise	Oxygen absorption significantly increased ($P<0.01$), serum lactate and heart rate significantly decreased ($P<0.05$) in both ginseng groups compared with placebo, no change of LH, testosterone and cortisol levels	Not reported
Forgo & Schimert (1985)	3	Placebo controlled; 2 parallel groups	28 healthy athletes 14/14 (range 20-30)	G 115 (100 mg twice daily)/placebo for 9 weeks	Oxygen uptake and heart rate during ergometer exercise, duration of effect	Oxygen uptake significantly increased ($P<0.05$) and heart rate significantly decreased ($P<0.01$) compared with plycebo; effects persisted at a 3-week follow-up assessment	Not reported
Cherdrungsi & Rungroeng. (1995)	4	Placebo-controlled; 4 parallel groups	41 healthy students 10/10/10/11 (range 19-26)	Standardised *Panax ginseng* extract (150 mg twice daily)/+exercise for 8 weeks	Maximal oxygen uptake during cycle ergometer exercise, leg muscle strength, body fat, resting heart rate	Body fat significantly decreased in both ginseng groups compared with baseline ($P<0.05$); subjects in the ginseng group without exercise improved maximal oxygen uptake, resting heart rate and leg strength compared with the placebo group without exercise ($P<0.05$)	None
Morris *et al.* (1996)	2	Placebo-controlled; cross-over	8 sportive volunteers 8/8 (mean 27)	Purified ethanolic *Panax quinquefolius* extract (618 mg or 1235 mg once daily/placebo for 1 week	Oxygen uptake, heart rate, time to exhaustion, mean lactate concentration, rating of perceived exertion during submaximal ergometer exercise	No significant intergroup differences in any of these outcome measures	Not reported

Dowling *et al.* (1996)	3	Placebo-controlled; 2 parallel groups	20 trained distance runners 8/8 (mean 37)	ESML (3.4 ml once daily)/placebo for 6 weeks	Oxygen uptake, respiratory exchange ratio, heart rate, lactate level and rating of perceived exertion during maximal ergometer exercise	No significant intergroup differences in any of these outcome measures	Not reported
Engels *et al.* (1996)	3	Placebo-controlled; 2 parallel groups	19 Healthy women 10/9 (range 21-35)	G 115 (100 mg twice daily)/placebo for 8 weeks	Maximal work performance, oxygen uptake, respiratory exchange rate, blood lactate, heart rate during graded cycle ergometry test to exhaustion	No significant intergroup differences in any of the measured parameters	None
Engels & Wirth (1997)	4	Placebo-controlled; 3 parallel groups	36 Healthy men 10/11/10 (mean: 23/26/27)	G 115 (400 mg daily)/G115 (200 mg daily)/placebo for 8 weeks	Oxygen consumption, respiratory exchange rate, heart rate, lactate concentration, rating of perceived exertion during graded ergometer exercise to exhaustion	No significant difference between ginseng and placebo groups in any of the measured parameters	Three cases of diarrhea in high dose ginseng group
Psychomotor performance and cognitive function							
Smith *et al.* (1995)	2	Placebo-controlled; 2 parallel groups	19 Healthy women 10/9 (mean 26)	G 115 (200 mg daily)/placebo for 8 weeks	Profile of mood states rating of perceived exertion after submaximal and maximal ergometer exercise	No significant intergroup differences in these parameters	Not reported
D'Angelo *et al.* (1996)	4	Placebo-controlled; 2 parallel groups	32 Male volunteers 16/16 (range 20-24)	G 115 (100 mg twice daily)/placebo for 12 weeks	Cancellation test, digit symbol substitution test, mental arithmetic test, choice reaction time	Significant intergroup differences (P<0.05) in favour of ginseng in mental arithmetic test	None
Sörensen & Sonne (1996)	4	Placebo-controlled; 2 parallel groups	127 healthy volunteers 55/57 (range: 40-70)	Standardised *Panax ginseng* extract (400 mg daily)/placebo for 12 weeks	Psychomotor tests, concentration, learning and memory, abstract thinking tests	Significantly better abstraction test in ginseng group compared with placebo (P<0.02)	None
Winther *et al.* (1997)	2	Placebo-controlled crossover; 4-armed study	24 Healthy volunteers sample size not reported (range: 36-58)	*Eleutherococcus senticosus* (625 mg twice daily)/(*Ginkgo biloba* (28.2 mg	Concentration test, selective memory test	Selective memory significantly improved compared with placebo (P<0.02)	Not reported

				flavonglycoside and 7.2 mg terpenlactone daily)/vitamins /placebo for 3 months			
Garcia (1988)	2	Comparative trial; 2 parallel groups	50 Elderly patients 26/24 (range 65-80)	Neurotrophic amino-acids + Vitamin B12 (dose not reported)/*Panax ginseng* extract (dose not reported) for 4 weeks	Association test, digit symbol test, inverted counting test	Ginseng was inferior compared with control in each of these parameters, association test and inverted counting test significantly improved (P<0.05) compared with baseline	Not reported
Immunomodulation							
Scaglione *et al.* (1990)	4	Placebo-controlled; 3 parallel groups	60 Healthy volunteers 20/20/20 (range 18-50)	G 115 (100 mg twice daily/aqueous ginseng extract (100 mg twice daily)/placebo for 8 weeks	Chemotaxis of polymorphonuclear leucocytes, percentage of total T-lymphocytes	Significant increase (P<0.05) of both parameters in both ginseng groups after 4 weeks and 8 weeks of treatment compared with baseline	Not reported
Srisurapanon *et al.* (1997)	3	Placebo-controlled; 2 parallel groups	20 Healthy males 10/10 (range 21-22)	Standardised ginseng extract (300 mg once daily)/placebo for 8 weeks	Total and differential leucocyte count, lymphocyte subpopulations CD3, CD4, CD8, CD4/8 ratio, CD19, CD25	No significant intergroup differences in any of these parameters	Not reported
Miscellaneous							
Sotaniemi *et al.* (1995)	3	Placebo-controlled; 3 parallel groups	36 Patients with type II diabetes mellitus 12/12/12 (mean 59/57/60)	Ginseng (100 mg once daily)/ginseng (200 mg once daily)/placebo for 8 weeks	Mood, vigour, psychophysical activity, fasting blood glucose levels	Significant (P< 0.05) improvement of mood, vigour, psychophysical activity and fasting blood glucose levels in both ginseng groups compared with baseline, significant (P<0.05) improvement of HbA_{1C} compared with baseline (ginseng 200 mg)	None
Williams (1995)	4	Placebo-controlled; 2 parallel groups	93 Volunteers of the Herpes Association 44/41 (not reported)	Elagen (400 mg once daily)/placebo for 6 months	Frequency, severity, duration of herpes episodes	75% of patients in the treatment group reported improvement in frequency, severity and duration with 34% in the placebo group	Tiredness (1/0); acid stomach (1/0); runny nose (0/2); headache (0/2)

Assessor's comment:

This systematic review focused on the evaluation of clinical studies on the efficacy of "ginseng root" extract in various indications that have been conducted until the late 1990s. Most of the studies investigated the standardized extract G115, but also studies on Eleutherococcus senticosus and Panax quinquefolius are included, which limits the overall conclusiveness. More recent clinical studies are evaluated in the systematic review by Lee & Son (2011).See above.

Coon & Ernst (2002): *Panax ginseng*, A systematic review of Adverse Effects and Drug Interactions

See section 5.1

Geng *et al*. (2010): Ginseng for Cognition

The objectives of this systematic review were to evaluate the efficacy and adverse effects of ginseng given to improve cognitive performance in healthy participants, participants with cognitive impairment or dementia. All relevant double-blind and single-blind randomized placebo controlled trials assessing the efficacy of ginseng on cognitive function were included. Healthy participants were cognitively intact to exclude dementia and mild cognitive impairment (MCI). Cognitive impairment was diagnosed using validated rating scales. Dementia was diagnosed by validated and reliable diagnostic criteria such as DSM-III, DSM-III-R, DSM-IV, NINDS-AIREN, NINCDS-ADRA and ICD-10.

Ginseng vs. placebo only and ginseng + routine treatment versus placebo + routine treatment have been considered as interventions. Routine treatment consisted of functional exercise, rehabilitation, nursing care and anti-dementia medications. In addition, compounds containing ginseng or active agents of the *Panax* genus as a major component have been considered.

The primary outcome measure was cognitive function (e.g. memory, concentration, immediate recall, calculation, speed of processing) as measured by psychometric tests such as Mini-Mental State Examination (MMSE), Randt Memory Test (RMT), Cognitive Subsection of the Alzheimer's disease Scale (ADAS-Cog).

A number of Secondary outcomes have been identified:

1. Behaviour disturbance (e.g. agitation, anxiety and restlessness) using validated rating scales such as the NPI and the CMAI.
2. Performance of activities of daily living measured by validated ratings scales, e.g. IADL
3. Global impression of change (clinical change or changes in severity of disease) using global rating scales such as ADCS-CGIC. Subjective perspective of family members or caregivers was also mentioned.
4. Quality of life, measured by recognised and validated quality of life scales or tools
5. Caregiver burden
6. Institutionalisation
7. Death
8. Acceptability of treatment as measured by withdrawal from trials
9. Incidence and severity of adverse effects.

Nine randomized, double-blind, placebo controlled trials [D'Angelo *et al.* (1986), Neri *et al.* (1995), Sotaniemi *et al.* (1995), Sørensen & Sonne (1996), Kennedy *et al.* (2001), Reay *et al.* (2005), Sünram-Lea *et al.* (2005), Kennedy *et al.* (2007, only abstract available), Kim J *et al.* (2008; combination product) primarily met the inclusion criteria. Eight enrolled healthy participants and one was of subjects with age-associated memory impairment (AAMI) (Neri *et al.* 1995). Only five [D'Angelo *et al.* (1986), Sørensen & Sonne (1996), Sünram-Lea *et al.* (2005), Kennedy *et al.* (2007, only abstract available), Kim J *et al.* (2008; combination product)] of the identified trials investigating the effects of ginseng on healthy participants had extractable information for efficacy and were included in the review. The average age of participants in three studies ranged from 20 to 31.3 years [D'Angelo *et al.* (1986), Sünram-Lea *et al.* (2005), Kennedy *et al.* (2007, only abstract available)], and in the other two studies [Sørensen & Sonne (1996), Kim J *et al.* (2008; combination product)] ranged from 51.4 to 59.4 years.

One study (Kim J *et al.* 2008) compared the effects of a preparation named HT008-1, a Korean ginseng complex comprising the roots of *Panax ginseng* and other components like *Scutellaria baicalensis*, *Angelica sinensis* and *Eleutherococcus senticosus* with placebo. Four studies compared the effects of ginseng extract with placebo [D'Angelo *et al.* (1986), Sørensen & Sonne (1996), Sünram-Lea et al. (2005), Kennedy *et al.* (2007, only abstract available)]. Of these four studies, two assessed the effects of G115 (D'Angelo *et al.* 1986, Sünram-Lea *et al.* 2005), one evaluated the effects of Gerimax Ginseng Extract (Sørensen & Sonne 1996), and one assessed the efficacy of Korean ginseng extract (Kennedy *et al.* 2007, only abstract availabe). For all of the included trials, ginseng products were administrated orally. The daily dose of ginseng extract ranged from 200 mg to 400 mg, whereas the daily dose of HT008-1 was 5200 mg. Four studies [D'Angelo *et al.* (1986), Sørensen & Sonne (1996), Kennedy *et al.* (2007, only abstract available); Kim J *et al.* (2008; combination product)] investigated the chronic effects of ginseng, with duration of treatment period varying from eight to twelve weeks. One study (Sünram-Lea *et al.* 2005) evaluated the acute effects of ginseng, with treatment duration of merely two days.

Fifteen reports were excluded because data on effects of ginseng could not be extracted, trials were not randomized, blinded or placebo controlled or due to other reasons.

Characteristics of included studies according to Geng et al. (2010):

D'Angelo *et al.* (1986)

Methods	Randomized, double-blind, placebo controlled trial.
Participants	Country: Italy Setting: Single center, University of Pavia Number of participants randomized: 32 (male) Number of participants completed: 32 (male) Age (years): 21.9 ± 1.6 (treatment), 21.7 ± 1.6 (control) Weight (kg): 69.5 ± 8.4 (treatment), 69.6 ± 10 (control) Inclusion criteria: All participants were students at a local University College and were in good physical condition as assessed by a medical examination and conventional laboratory tests Exclusion criteria: Not stated. Baseline performance were similar in the two groups as tested by psychometric tests except the choice reaction time. Choice reaction time was longer in the G115 group
Interventions	Comparison: G115 versus placebo 1. G115® (GINSANA, Pharmaton S.A., Switzerland): One capsule twice a day, taken at 8:00 and 13:00, corresponding to a total daily dose of 200mg 2. Placebo: Identical lactose-containing capsules 3. Duration of treatment: 12 weeks
Outcomes	1. Tapping test 2. Simple reaction time 3. Choice reaction time 4. Cancellation test 5. Digit symbol substitution test 6. Mental arithmetic 7. Logical deduction 8. Tolerability outcomes
Notes	1. This study was the first randomized, double-blind placebo-controlled study aimed at investigating the effect of G115 on some aspects of cognitive function in healthy volunteers 2. Changes in psychometric test score from baseline to the final assessment were not suggested in the report 3. The trial lacked an adequate description of methods of randomization and blinding 4. We contacted Dr Emilio Perucca on 28 May 2009 for additional information

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	Unclear	Allocation concealment was not mentioned and whether the sequence was concealed remained unclear
Blinding? All outcomes	Yes	Both experimenters doing the tests and participants were blinded
Incomplete outcome data addressed? All outcomes	Yes	All participants completed the study.

Sørensen & Sonne (1996)

Methods	Randomized, double-blind, placebo-controlled trial.
Participants	Country: Denmark Setting: Single center, Department of internal medicine, Gentofte University Hospital Number of participants randomized: 127 Number of participants completed: 112 (38 male) Age (years): 51.4 ± 7.9 (treatment), 51.5 ± 9.1 (control) Schooling (years): 10.5 ±1.9 (treatment), 10.2 ± 1.9 (control) Advanced education: 78% (treatment), 82% (control) Inclusion criteria: Healthy volunteers older than 40 years. Exclusion criteria: Serious illness, diseases of the central nervous system, and abuse of alcohol or drugs. Participants receiving psychoactive medication that might interact with ginseng For all of the tests except the Selective Reminding Test, the baseline values for the two groups were similar and corresponded to the high end of expected values for normally functioning participants
Interventions	Comparison: Gerimax Ginseng Extract versus placebo 1. Gerimax Ginseng Extract (Dansk Droge A/S, Ishøj, Denmark): 400 mg per day 2. Placebo: Inactive, heavily soluble calcium preparation identical with the Gerimax 3. Duration of treatment: 8 to 9 weeks
Outcomes	1. Simple Auditive Reaction Times Test 2. Simple Visual Reaction Times Test 3. Finger-Tapping Test 4. D2 Test 5. Fluency Test 6. Selective Reminding Test 7. Logical Memory and Reproduction Test 8. Rey-Oestrich Complex Figure Test 9. Wisconsin Card Sorting Test 10. Tolerability outcomes
Notes	1. The study was supported by a grant from Dansk Droge A/S (Ishøj, Denmark) 2. A comprehensive battery of cognitive tests was used to investigate cognitive function in healthy, middle-aged participants 3. The trial lacked an adequate description of methods of randomization 4. Allocation concealment was not mentioned in the report. 5. We contacted Dr Jesper Sonne on 28 May 2009 for additional information

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	A randomization code was made by a pharmacist in the company and the method of randomization code generation was unclear
Allocation concealment?	Yes	The randomization code was kept under lock until all results had been analysed. Not till then was the treatment allocation revealed. Members of the company were in no way involved in the conduct of the trial and had absolutely no access to participants or test procedures etc
Blinding? All outcomes	Yes	Both participants and study managers were blinded.
Incomplete outcome data addressed? All outcomes	Yes	15 (12%) dropped-out, 6 due to illness and 9 for unknown reasons. Compliance was assessed by querying the participants and by counting the tablets returned. In no case did the returned tablets exceed 5% of the total number distributed to the participants

Sünram-Lea *et al.* (2005)

Methods	Randomised, double-blind, placebo-controlled, two period cross-over design
Participants	Country: UK Setting: Single University center Number of participants randomized: 30 (15 male) Number of participants completed: not given Age (years): 18-25 (Mean: 20) Inclusion criteria: Healthy undergraduate young volunteers taking no medication or herbal supplements. Of the 30 participants two were light smokers (<5 cigarettes per day and <2 per week, respectively). Participants agreed to refrain from smoking, and caffeine and alcohol consumption throughout each study day. No other dietary restrictions were implemented Exclusion criteria: Not stated
Interventions	Comparison: G115 versus placebo 1. G115® (Pharmaton S.A., Switzerland): 400 mg
	2. Placebo 3. Subjects received two capsules of identical appearance, each containing either 200mg G115 or an inert placebo, in a counterbalanced order, with a seven-day washout period between treatments 4. Duration of treatment: 2 days
Outcomes	1. Primary outcome measures (a) Quality of memory factor (b) Speed of memory factor (c) Speed of attention factor (d) Accuracy of attention 2. Secondary outcome measures (a) Working memory sub-factor (b) Secondary memory sub-factor (c) CDR factor scores
Notes	1. The fourth author Petrini O was employed by Pharmaton SA, the producer of the standardised ginseng extract G115 used in the trial 2. The trial aimed to evaluate the effect of ginseng (400 mg) administration on cognitive performance and mood in healthy young volunteers 3. Methods of blinding and adverse effects of G115 were not stated in the report 4. We contacted Professor Keith A. Wesnes on 21 July 2009 for additional information

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A person not involved in the trial carried out randomisation manually using a randomisation table
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Subjects and test administrators were blinded.
Incomplete outcome data addressed? All outcomes	Unclear	Exact number of participants completed the study was not stated. However, from the degree of freedom in the paired T-test we concluded that authors used number of participants randomized to calculate the results

Kennedy *et al.* (2007)

Methods	Randomized, double-blind, placebo-controlled, two period cross-over design
Participants	Country: UK Setting: Single University center Number of participants randomized: 18 (5 male) Number of participants completed: 16 Age (years): 38.31 ± 10.3 Inclusion criteria: Healthy undergraduate young volunteers taking no illicit social drugs, and were free from “over the-counter” or prescribed medications, with the exception, for some female volunteers, of the contraceptive pill. Participants fasted overnight and were alcohol and caffeine free for 12 hours prior to all assessment sessions, and also abstained from psychoactive products during the testing day Exclusion criteria: Heavy smokers (>5 cigarettes/day). No significant differences between all baseline assessments on all measures within the study
Interventions	Comparison: Korean Panax ginseng extract versus placebo 1. Korean Panax ginseng extract (Cheong Kwan Jang, Korea Ginseng Corporation, Seoul, Republic of Korea): 200 mg 2. Placebo: Apparently identical with the intervention drug 3. Each participant took either ginseng or placebo for 8 weeks, with a 4 week placebo washout period between treatment arms 4. Duration of treatment: 8 weeks
Outcomes	1. Cognitive Drug Research (CDR) computerised assessment battery 2. Working Memory Tasks (a) Corsi Block Tapping task (b) 3-back task (c) Alphabetic working memory 3. Subjective mood and 'quality of life' measures (a) Bond-Lader Mood scales (b) World Health Organisation Quality of Life questionnaire-BREF: (WHOQOL-BREF) 4. Blood glucose parameters
Notes	1. The effects of Korean ginseng extract (200 mg) on cognitive performance, gluco-regulatory parameters and ratings of subjective mood and 'quality of life' were investigated 2. Detailed information of the Korean ginseng extract were not given in the report 3. The report lacked an adequate description of randomization, blinding, reason of drop-outs and adverse effects of Korean ginseng extract 4. Authors did not analyse results of the first treatment period after randomization as it would have too little statistical power to be interpretable 5. We contacted Professor David Kennedy on 27 May 2009 and Dr Jonathon Reay on 8 July 2009 for additional information

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number generator allocating participants to two groups
Allocation concealment?	Yes	All treatments were packaged and coded by a disinterested third party, who retained the emergency code break for use in the event of any serious adverse events
Blinding? All outcomes	Yes	Participants and all experimenters were blinded.
Incomplete outcome data addressed? All outcomes	Yes	Two participants failed to complete the trial (16 evaluable sets of data). Reasons unrelated to treatment i.e. simply dropped out of the study, and as it was an extended treatment period they did not have time to replace them

Kim J *et al.* (2008)

Methods	A randomized, double-blind, fixed-dose, placebo-controlled, parallel group trial
Participants	Country: South Korea Setting: Single University center, Kyung Hee University Medical Center Number of participants randomized: 118 (42 male) Number of participants completed: 99 Age (years): 59.4 ± 5.1 (treatment), 59 ± 5 (control) Schooling (years): 12.2 ± 3.4 (treatment), 11.3 ± 2.9 (control) Inclusion criteria: Cognitively intact adults were required to have completed six or more years of education and have no difficulty reading or writing. A score≥borderline scores of 16.9 at ages 65 to 84 or 18.9 at ages 55 to 64 on the memory subscale of the Korean-Dementia Rating Scale (K-DRS) and a score of >24 on the Korean Version of the Mini Mental State Examination (MMSE-K) Exclusion criteria: Individuals who had histories of neurological disorders, including stroke, head injury, psychiatric disorders (mental retardation, schizophrenia, depression with ≥21 on the Beck's Depression Inventory (BDI) scores), drug abuse, alcohol dependence/abuse, or a disease or surgery that could influence drug absorption, were excluded from this study before the K-DRS test or MMSE-K test. Individuals who were being treated with hormones, antidepressants or other psychoactive medications, who had internal medical problems on blood test (except stable hypertension or diabetes mellitus with medication), who had an unstable medical state, were pregnant or would become pregnant, were undernourished, or who drank more than eight cups of coffee per day also were excluded. Participants who had participated in other clinical trials in the last month were also excluded. Participants were excluded from the study if they did not take more than 8 packs of study medicines in any 2-week period No significant differences between all baseline assessments on all measures within the study

Kim J *et al.* (2008) continued

Interventions	Comparison: HT008-1 versus placebo 1. HT008-1 (Lot. No.001) (NeuMed Inc., Korea): two pouches daily with a daily dose of 5200mg (an average of 100 mg/ kg). In this clinical study, HT008-1 was prepared as a liquid containing 2600 mg of standardized extracts in a 30 ml pouch of solution 2. Placebo: two pouches daily that did not differ in appearance (e.g., color, size, smell, or taste) from HT008-1 3. Duration of treatment: 8 weeks
Outcomes	1. Wechsler Memory Scale-III (WMS-III) (a) Logical memory I (b) Logical memory II (c) Verbal paired associates I (d) Verbal paired associates II (e) Letter-Number Sequencing (f) Spatial span (g) Auditory recognition delayed 2. World Health Organization Quality of Life Assessment Instruments-BREF (WHO-QoL-Bref) (a) Overall quality of life (b) General health (c) Physical health (d) Psychological health (e) Social relationships (f) Environment 3. Tolerability outcomes
Notes	This work was supported by a grant (PF 0320201-00) of Plant Diversity Research Center of 21st Century Frontier Research Program (Ministry of Science and Technology, Korea) , and by grants from the Seoul R&D Program (10524) and the Second Stage of Brain Korea 21 Project (Ministry of Education, Korea)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Through the online service of www.randomizer.org.
Allocation concealment?	Yes	Through the online randomization service.
Blinding? All outcomes	Yes	To analyze the blinding efficacy, participants were asked to which group they belonged. It could be concluded that blinding was not broken from the testing result
Incomplete outcome data addressed? All outcomes	Yes	Number (or %) of followed-up from each group: HT008-1 (50/59, 85%), Placebo (49/59, 83%); Reasons for loss: HT008-1 (4-lost to follow up, 1-adverse events, 4-protocol violation), Placebo (5-lost to follow up, 2-adverse events, 3-protocol violation)

Adverse effects:

No adverse effects were identified in two trials (D'Angelo *et al.* 1986, Sørensen & Sonne 1996) according to the reports. No adverse effects were found in the study by Kennedy *et al.* (2007, only abstract available) based on information provided by the leading author. It should be mentioned that results from one study (Kim J *et al.* 2008; combination product) which investigated the efficacy of HT 008-1 revealed some adverse effects in both, the HT008-1 group and the placebo group including headache, dizziness, diarrhea, constipation, vomiting, gastric complaints, and dermatitis or eczema. However, no serious adverse events were reported during the study and no causal relationship was determined between the HT008-1 treatment and any adverse event.

Overall, ginseng extracts seemed to have beneficial effects for improvement of some aspects of cognitive function, behaviour and quality of life in healthy participants. No serious adverse events caused by the investigated ginseng preparations were found. For cognitive function results of data analysis suggested the improvement in one aspect of working memory, one aspect of speed of processing, in two aspects of psychomotor performance, and in one aspect of learning and memory. However, the authors concluded that results of the analysis should be interpreted with caution. Small sample size (289 participants) might contribute to insufficient power to detect a difference, if one was present. Results were based on data from a single trial which had not been duplicated by other trials. This may limit the strength of the evidence. There was a wide range of instruments utilized to measure various aspects of cognition within individual trials, which caused problems with the multiple comparisons of cognitive outcomes. The effects of ginseng were observed in short term, varying from 2 days to 12 weeks. The authors suggested that trials with longer duration of treatment and follow-up are needed for investigation of the long-term benefit.
The review aimed to assess the effects of ginseng for healthy participants, participants with cognitive impairment or any type of dementia of any severity. But only young and mid-aged healthy participants with extractable data for the analysis were included. Therefore, conclusions about cognitive impairment and dementia cannot be made. However, participants in two excluded trials were AD [Heo *et al.* (2008), Lee ST *et al.* (2008, only abstract available)], for characterization of these RCTs see tables below:

Heo *et al.* (2008):

Heo 2008	Randomized, open-label pilot study to evaluate the adjunctive effect of Korean red ginseng (KRG) in AD Results: Participants in the high-dose (9 g/day) KRG group showed significant improvement on the ADAS and CDR after 12 weeks of KRG therapy when compared with those in the control group. Both low-dose (4. 5 g/day) and high-dose (9 g/day) KRG groups showed improvement from baseline MMSE when compared with the control group, but this improvement was not statistically significant. Two participants in the low-dose KRG group complained of feeling feverish and two participants in the high-dose KRS group complained of nausea Conclusions: KRG showed good efficacy for the treatment of AD; however, further studies with larger samples of participants and a longer efficacy trial should be conducted to confirm the efficacy of KRG Reasons for exclusion: This was not a blinded study. The trial compared KRG as an adjuvant therapy to conventional anti-dementia medications, not placebo controlled trial

Lee ST *et al.* (2008)

Lee 2008	Randomized, open-label prospective study to evaluate clinical efficacy of Panax ginseng in the cognitive performance of AD participants Results: After 12 weeks of the Panax ginseng powder (4.5 g/d) treatment, the cognitive subscale of ADAS and the MMSE score began to show improvements and continued up to 12 weeks. At 12 weeks after the ginseng discontinuation, the improved ADAS and MMSE scores declined to the levels of the control group. The adverse events (e.g. heat-sense, dizziness, nausea, anorexia, diarrhea and headache) were mild and transient Conclusions: Panax ginseng was clinically effective in the cognitive performance of AD participants Reasons for exclusion: This was an open-label trial with no blinding performed. Both Ginseng group and control group continued the conventional therapy, not placebo controlled trial

Assessor's comment:

The systematic review includes five randomized controlled clinical trials of good methodological quality. In four of them Panax ginseng preparations (in two cases G115) were investigated in validated test systems. In some aspects the investigated ginseng extracts showed favourable effects on cognitive function and psychomotor function, thus supporting the plausibility of the traditional use of Panax ginseng to improve concentration, but data is not sufficient to propose well-established use in this indication.

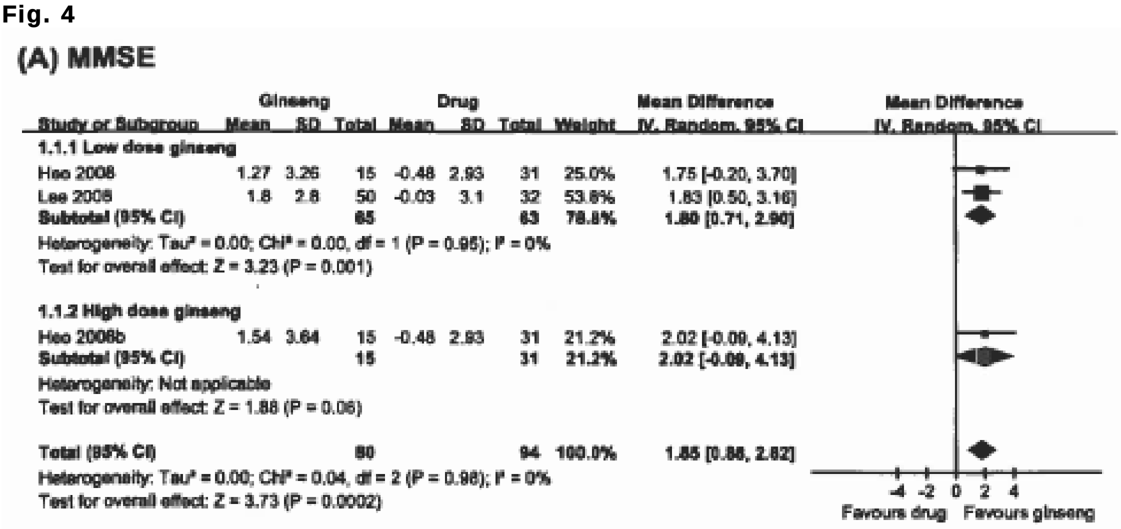
Lee MS *et al*. (2009): Ginseng for Cognitive function in Alzheimer's Disease: A systematic review

The objective of this systematic review was to assess the clinical evidence for or against ginseng as a treatment for Alzheimer's disease (AD). Randomized clinical trials that reported on the treatment of human AD patients with *Panax ginseng*, either as the sole treatment or as an adjunct to conventional treatments were included. Only two RCTs [Heo *et al.* (2008), Lee ST *et al.* (2008, only abstract available)], originating from Korea, met the inclusion criteria. One adopted a two-arm and the other a three-arm parallel group design. The two trials included a total of 158 AD patients, which had been diagnosed according to National Institute for Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and related Disorder Association criteria. One RCT (Lee ST *et al.* 2008) employed white ginseng, and the other one (Heo *et al.* 2008) used red ginseng for treatment as an adjunct to conventional drug therapy in both studies. Heo *et al.* (2008) reported donepezil (5-10 mg/d), galantamine (16-24 mg/d), memantine (20 mg/d) or rivastigmine (6-12 mg/day) for conventional drug therapy. Lee ST *et al.* (2008) did not report the conventional medication in detail. The doses were 4.5 or 9.0 g of powdered drug daily for 12 weeks. The outcome measures in these trials were MMSE, ADAS, and Clinical Dementia rating (CDR, only Heo *et al.* 2008).

<u>Outcomes:</u>

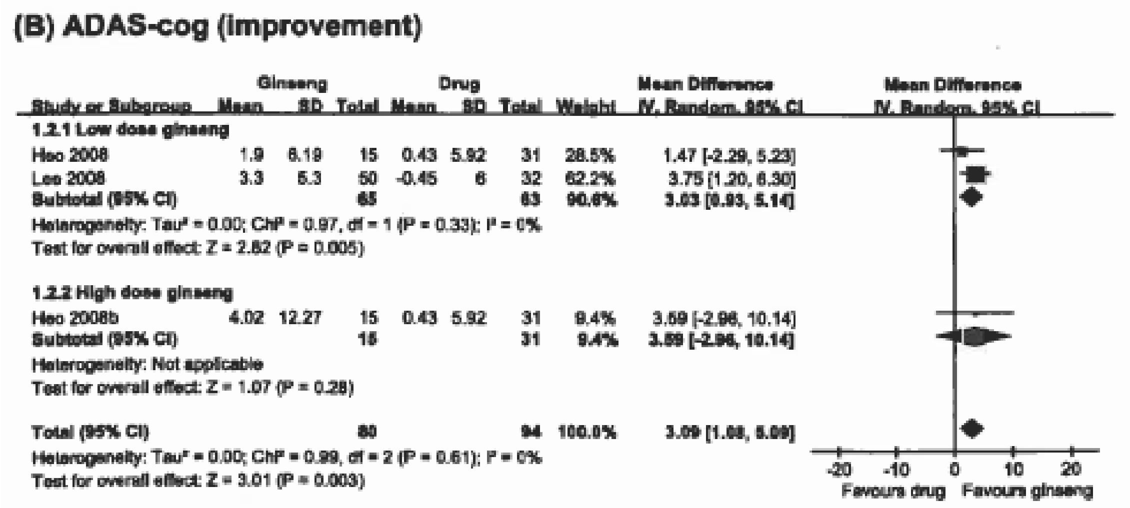
- MMSE: High dosages of red ginseng (9 g/day) significantly improved MMSE compared with conventional therapy after 12 weeks while a low dose of red ginseng (4.5 g/day) failed to do so. Low dose of white ginseng (4.5 g/day) showed favourable effects compared with standard drug therapy after 4 weeks and 12 weeks. The meta-analysis of these data showed a significant effect. Subgroup analysis also suggested favourable effects of ginseng in doses of 4.5 g/d. (**Fig. 4**)

Fig. 4



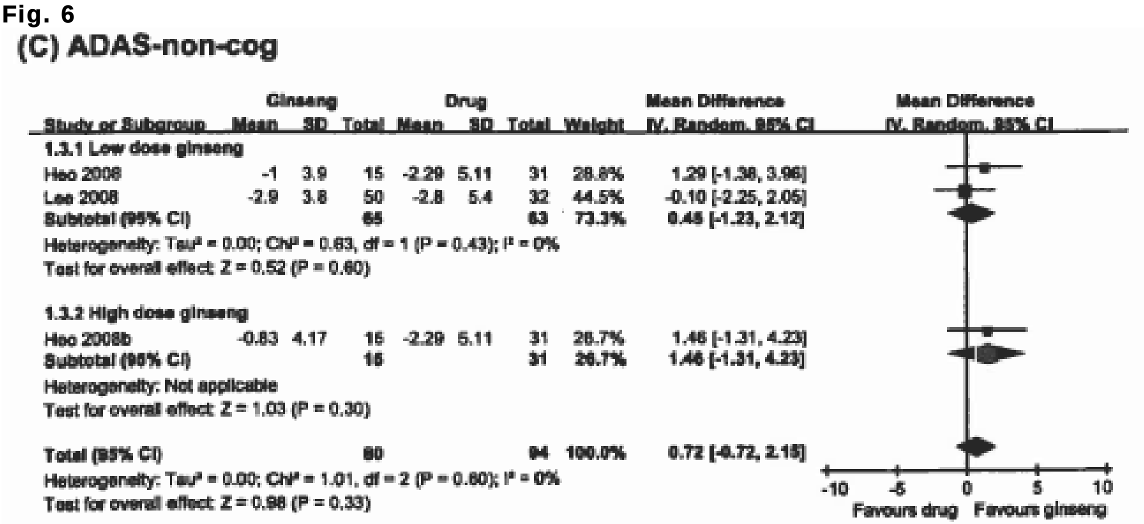
- ADAS cognitive function: One RCT showed significant effects of white ginseng on ADAS-cognitive subscale after 4 and 12 weeks. The other RCT failed to do so for red ginseng. The meta-analysis of the RCTs suggested ginseng plus conventional drugs to be superior to conventional drugs alone in improvement of ADAS cognitive subscale. Subgroup analysis also suggested favourable effects of ginseng in doses of 4.5 g/d. (**Fig. 5**)

Fig. 5



- ADAS non-cognitive function: Both RCTs failed to show favourable effects. Subgroup analysis also failed to show the superior effects of ginseng in dose of 4.5 g/d. (**Fig. 6**)

Fig. 6



Conclusions:

Lee MS *et al*. (2009) concluded that even though positive effects had been observed in higher dosages for the treatment with ginseng in addition to conventional medication in AD patients, firm conclusions could not be drawn. Both RCTs showed deficiencies in methodological quality (Jadad score 1), e.g randomization methods and concealment of treatment allocation were not reported, neither subject nor assessor blinding were done. Furthermore, it was not clear whether validated questionnaires had been employed. Finally, the small sample size of 158 AD patients also might limit the conclusiveness of this systematic review.

Assessor's comment:

The type of ginseng preparation is not reported correctly in the systematic review. Preparations are referred to as dried ginseng extract, whereas in the original publications of the RCTs it is clearly stated that the powdered roots were used. However, as Lee MS et al. (2009) state, the ginseng treatment was conducted in addition to the conventional treatment in AD patients. Although in higher dosages a positive effect was seen for ginseng treatment, due to the low methodological quality (no blinding!) and the small number of patients included in the studies data is not sufficient to propose well-established use in this indication.

Buettner *et al*. (2006): Systematic review of the effects of ginseng on cardiovascular risk factors

The objective of this systematic review was to examine the evidence fof the efficacy of ginseng on cardiovascular risk factors including blood pressure, lipid profiles, and blood glucose, and to summarize reported cardiovascular adverse events. Published human clinical trials of any duration evaluating Panax sp. (*Panax ginseng*, i.e. "Korean ginseng" *and Panax quinquefolius*, i.e. "American ginseng"), used as a monopreparation or as a primary component of combination preparation, that reported outcomes on blood pressure [Caron *et al.* (2002), Sung *et al.* (2000, only abstract available), Cherdrungsi & Rungroeng (1995, only abstract available), Han *et al.* (1998, only abstract available), Kaneko *et al.* (1984, original article not available)], cholesterol [Kim & Lee (2001), Sotaniemi *et al*. (1995), Kim SH *et al.* (2003), Punnonen & Lukola (1984, only abstract available), Yamamoto *et al.* (1983, only abstract available), Yamamoto & Kumagai (1984, original article not available)], and/or serum glucose [Sotaniemi *et al.* (1995), Scaglione *et al.* (1996), Hallstrom *et al.* (1982, original article not available), Okuda & Yoshida (1980, original article not available), Sievenpiper *et al.* (2004), Sievenpieper *et al.* (2003a), Sievenpiper *et al.* (2003b; *Panax quinquefolius*)], were included. Randomized controlled trials (RCTs) and nonrandomized studies (NRSs) as well as dissertations and symposia proceedings, if they were published in complete form, were reviewed. Case reports were not included in the systematic review but additionally screened for possible cardiovascular adverse events. All potentially relevant studies with English abstracts were evaluated for inclusion/exclusion criteria but only articles with full text available in English were reviewed.
Altogether 31 articles were identified, reporting results for blood pressure, cholesterol and/or serum glucose. Of these, 22 studies were RCTs, published as 19 articles and 1 dissertation. Twelve NRSs were published as 9 articles and 3 symposia proceedings. Ginseng treatments were compared with placebo in 20 studies, potential active controls in 3 studies and no treatment in 10 studies. Most studies evaluated the effects of *Panax ginseng* preparations, 16 as monopreparations and 9 as combination preparations.
Less than half of the trials were of high methodological quality. Most studies were small, with <30 subjects. Three studies included >100 subjects [Caso Marasco *et al.* (1996, combination product, only abstract available), Yuan *et al.* (1997, combination product, only abstract available), Scaglione *et al.* 1996). Nine studies reported using standardized preparations or used products commonly known to be standardized, and 8 studies reported testing and/or provided ginsenoside profiles of the preparations.

<u>Effects on blood pressure:</u>
Twelve studies included blood pressure outcomes, most evaluated *Panax ginseng* preparations (5 monos, see **Table 3**). Participants included subjects with hypertension, coronary heart disease, congestive heart failure, type 2 diabetes, and healthy subjects, or those without major illnesses described. Ginseng doses administered varied from 40 mg to 4.5 g per day. Eight studies were conducted over periods ranging from 4 weeks to 27 months, with many demonstrating slight reductions of ≤ 4% in systolic blood pressure and/or diastolic blood pressure compared with placebo or

control. The majority of these changes were not considered statistically significant. Two of four acute single-dose studies demonstrated larger decreases in systolic and diastolic blood pressure compared with baseline (8-11%). In one of these studies, the same subjects were examined in a subsequent RCT with placebo control, and only slight reductions (1-4%) in systolic and diastolic blood pressure were observed compared with placebo, which did not reach statistical significance defined in their study. The authors suggested that the more substantial reductions in blood pressure observed in the uncontrolled trial might have been due in part to diurnal variation in blood pressure. Three studies demonstrated slight elevations in blood pressure of 1-2% compared with placebo, and of 4% compared with baseline, which were not considered statistically significant by any study.

Table 3: Short description of studies evaluating effects of *Panax ginseng* monopreparations on blood pressure

Reference	Design/ Jadad score	Subjects (mean age, y)	Ginseng dose (% ginsenoside)/ Manufacturer/duration of treatment	Effect change
Caron *et al.* (2002)	RCT/4	30 healthy, 15 ginseng, 15 control (22y)	*Panax ginseng* extract, 200 mg/day (4%) vs. Placebo (lactose monohydrate)/Pharmaton, Ridgefield, CT/ 4 weeks	Compared with placebo SBP -0.5% (p=0.83) DBP +2% (p=0.68)
Sung *et al.* (2000)	RCT/4	17 HTN, 10 ginseng, 7 control (59 y)	*Panax ginseng*, 1.5 g tid; 4.5 g/day vs. no treatment/21-27 months	Compared with baseline, not significant
Han *et al.* (1998)	NRS	45 HTN; 8 w/ white-coat HTN, 26 w/ essential HTN	*Panax ginseng*, 1 g tid, 3 g/day, no control;/Korean Tobacco & Ginseng/Korea/ 8 weeks	Compared with baseline, white coat HTN: SBP -5% (p=0.40), DBP -4% (p=0.21); essential HTN: SBP -5%(p=0.03), DBP -4% (p=0.17)
Cherdrungsi & Rungroeng (1995,abstract only)	RCT/4	41 healthy; 10 ginseng, 10 control; 10 ginseng, 11 control (range 19-26 y)	*Panax ginseng* extract 300 mg bid, 600 mg/day vs. placebo/New Century Pharma, Seoul, Korea/8 weeks (no training); 300 mg bid vs. placebo / 8 weeks (with physical training)	Compared with placebo; no training: SBP +1% (p=0.71), DBP NS; training: SBP +2% (p=0.560) DBP +2% (p=0.64)
Kaneko *et al.* (1984,original article not available)	NRS; single dose study	24 healthy (30 y)	*Panax ginseng* 4.5 g given 1 h prior to exercise test vs. exercise alone/Korean Office of Monopoly Seoul	Compared with control SBP -8% (p<0.01), DBP -11% (p<0.01)

RCT= randomized controlled trial, NRS= nonrandomized study, HTN= hypertension, SBP=systolic blood pressure, DBP=diastolic blood pressure

<u>Effects on cholesterol:</u>

Nine studies evaluated cholesterol outcomes over periods ranging from 7 days to 3 months. Monopreparations of *Panax ginseng* were used in 6 studies (see **Table 4**). Participants included subjects with hyperlipidemia, type 2 diabetes, healthy subjects, postmenopausal women or smokers. Most studies were small, including treatment groups ranging from 3 to 24 subjects. Ginseng doses varied from 100 mg to 6 g per day, in most cases preparations were not standardized. Overall results were inconsistent; however, 3 studies demonstrated improvement in one or more lipid parameters that was statistically significant compared with baseline values [Kim SH (2003), Yamamoto (1983, only abstract available), Yamamoto (1984)].

Table 4: Short description of studies evaluating effects of *Panax ginseng* monopreparations on blood lipids

Reference	Design/ Jadad score	Subjects (mean age, y)	Ginseng dose (% ginsenoside)/ Manufacturer/duration of treatment	Effect change
Kim SH *et al.* (2003)	NRS	8 healthy male students (21 y)	*Panax ginseng* extract 2 g tid, 6g /day/ ILWha Co. Ltd., Kyonggi, Korea/ 8 weeks	Compared with baseline: TC -12% ($p<0.05$) HDL +44% ($p<0.05$) LDL -45% ($p<0.05$) TG -24% ($p<0.05$)
Kim *et al.* (2001)	RCT/3	15 male smokers; 3 ginseng, 3 vitamin E, 3 beta-carotene, 3 vitamin C, 3 control (24 y)	*Panax ginseng* 1.8 g/day vs. placebo/Korea Tobacco & Ginseng, Daejon	Compared with placebo: TC +2% ($p>0.05$) HDL +30% ($p>0.05$) LDL -29.7 ($p>0.05$) TG +10.5 ($p>0.05$)
Sotaniemi *et al.* (1995)	RCT/3	36 type 2 DM, 12 ginseng 100 mg (59y), 12 ginseng 200 mg (57 y), 12 ginseng control (60 y)	*Panax ginseng* (preparation not specified) 100 mg/day vs. 200 mg/day vs. placebo	100 mg compared with placebo: TC +4% ($p=0.69$) HDL +9% ($p=0.42$) LDL +3% ($p=0.83$) TG -17% ($p=0.42$) 200 mg compared with placebo: TC +7% ($p=0.40$) HDL +0% ($p=1.0$) LDL +11% ($p=0.44$) TG -21% ($p=0.20$)
Punnonen & Lukola (1984)	NRS	15 postmenopausal participants (59y)	*Panax ginseng* 250 mg bid; 500 mg/day /12 weeks	Compared with baseline: all values not significant
Yamamoto & Kumagi (1984, original article not available)	NRS	67 hyperlipidemia (age not reported)	*Panax ginseng* 2.7 g/day/ Korean Office of Monopoly Up to 24 months	Compared with baseline: TC not significant HDL +7% ($p<0.05$) TG -29% ($p<0.01$)
Yamamoto *et al.* (1983)	NRS	11 participants: 5 normal lipids, 6 hyperlipidemia (40y)	*Panax ginseng* 1.5 g tid; 4.5 g/day (2-5%) /Japan-Korea Red Ginseng Co.; Ltd., Kobe Japan	Compared with baseline: TC not significant HDL +7-9% ($p<0.05$) TG not significant, -29% in hyperlipidemic participants

RCT= randomized controlled trial, NRS= nonrandomized study, TC=total cholesterol, HDL=high density lipoprotein, LDL=low density lipoprotein, TG=total triglycerides

Effects on blood glucose:

Fifteen studies evaluated the effects of ginseng on blood glucose. Seven thereof examined preparations of *Panax ginseng* (see **Table 5**), the others evaluated *Panax quinquefolius*. Six studies were conducted over periods of 3 days to 3 months, four of them with *Panax ginseng*. Two studies examined the effects of acute single-dose administrations of *Panax ginseng*, six studies evaluated *Panax quinquefolius* and one study evaluated seven different types of *Panax* species mono-preparations. Participants included subjects with diabetes, without diabetes or described as “healthy” and volunteers recommended to receive flu vaccine. One study (Okuda & Yoshida 1980, original article not available) involved administering ginseng to 21 patients with diabetes who were using insulin. Most studies were small with treatment groups of 36 or fewer subjects. Overall three of the studies conducted with *Panax ginseng* preparations found blood glucose-lowering effects. Three acute studies conducted with *Panax ginseng* demonstrated either no change in blood glucose (Sievenpiper *et al.* 2003a, b) or increased postprandial blood glucose (Sievenpiper *et al.* 2004).

Table 5: Short description of studies evaluating effects of *Panax ginseng* monopreparations on blood glucose

Reference	Design/ Jadad score	Subjects (mean age, y)	Ginseng dose (% ginsenoside)/ Manufacturer/duration of treatment	Effect change
Scaglione *et al.* (1996)	RCT/4	227 participants receiving flu vaccine; 114 ginseng, 113 control (48y)	*Panax ginseng* extract 200 mg/day (4%) vs. placebo /12 weeks	Compared with placebo BG +3% (p=0.07)
Sotaniemi *et al.* (1995)	RCT/3	36 type 2 DM; 12 ginseng 100 mg (59 y), 12 ginseng 200 mg (57 y), 12 control (60 y)	*Panax ginseng* (preparation not specified) 100 mg/day vs. placebo 200 mg/day vs. placebo/ Dansk Droge, Copenhagen, Denmark/ 8 weeks	Compared with placebo: 100 mg: FBG -7% (p<0.05) HbA_{1c} 0% (p=NS) 200 mg: FBG -10% (p<0.05) HbA_{1c} -8% (p<0.05)
Hallstrom *et al.* (1982)	NRS (crossover)	12 nurses (21-27 y)	*Panax ginseng* 1200 mg/day vs. placebo/ 3 days	Compared with placebo: BG -13% (p=0.02)
Okuda & Yoshida (1980, original article not available)	NRS	21 DM patients (age not reported)	*Panax ginseng* 2.7 g/day /Nikkan Korai, Ninjin, Japan/3 months	Compared with baseline: Improved BG control in 8 of 21 subjects, p values not reported
Sievenpiper *et al.* (2004)	RCT; crossover/4; single dose study	12 participants, DM (34 y)	Various ginsengs, among them Asian and Asian red ginseng, all 3 g vs. placebo (comflour) 40 min before OGTT	AUC compared with placebo: Asian ginseng: +37.2% (p=0.005) Asian red ginseng: +3.9% (p>0.05)
Sievenpiper *et al.* (2003a)	RCT, crossover/2, single dose study	11 students (29 y)	*Panax ginseng* 1,2 or 3 g (0.8%)/Ministry of Agriculture, South Korea vs. placebo (comflour),/ 40 min before OGTT	AUC compared with placebo: not significant in any case (p=0.9)
Sievenpiper *et al.* (2003b)	RCT, crossover/2	11 students (27y)	*Panax ginseng* 1,2 or 3 g (0.8%)/Ministry of Agriculture, South Korea vs. placebo (comflour),/40 min	AUC compared with placebo: not significant in any case (p=0.13)

			before OGTT	

RCT= randomized controlled trial, NRS= nonrandomized study, DM=diabetes mellitus, BG=blood glucose, FBG=fasting blood glucose, HbA_{1c}= glycosylated hemoglobin, OGTT= oral glucose tolerance test

Adverse events:
Only few reports of adverse events were found in the studies reviewed, with gastrointestinal effects being most common. However, because 40% of the studies had no statement on adverse effects, such effects could be underreported.

The authors concluded that at that time evidence did not support the use of ginseng to prevent or reduce cardiovascular risks. There was no consistent evidence that ginseng lowered blood pressure. On the other hand, there was little evidence to support an effect of ginseng in elevating blood pressure, as discussed in reports on the "ginseng abuse syndrome" (Siegel 1979, Siegel 1980, Chen 1981). Preliminary NRSs suggested that Ginseng might have an effect on improving lipid profiles but RCTs designed to evaluate the effect of ginseng on lipids as primary outcome were lacking. Study results on the effect of *Panax ginseng* on blood glucose levels were inconsistent and did not allow firm conclusions.

Assessor's comment:
The systematic review included studies on the powdered herbal substance and extracts of Panax ginseng as well as Panax quinquefolius and combination products which limits the overall conclusiveness. With focus on the studies evaluating the clinical effects of Panax ginseng on blood pressure, cholesterol and blood glucose it can be stated that the results are inconsistent. Most of the studies have shortcomings concerning methodology or include only a small number of patients and pooling is rather difficult/impossible due to the heterogeneity of the studies. There is no consistent evidence that Panax ginseng influences cardiovascular risk factors such as elevated blood pressure, blood lipids or blood glucose in a positive way. Furthermore Panax ginseng has not been in medicinal use in these indications, and therefore, well-established use is not proposed. Nevertheless, positive results in small studies with good methodological quality show that Panax ginseng might have regulative and slightly activating properties on metabolic parameters. Therefore it can be supportive in situations of decreased physical capacity such as fatigue and weakness as proposed for the traditional use indication.

Krebs Seida *et al.* (2011): North American (*Panax quinquefolius*) and Asian Ginseng (*Panax ginseng*) Preparations for Prevention of the Common Cold in Healthy Adults: A systematic review

The objective of this systematic review was to assess the efficacy of ginseng preparations for the prevention of common colds in healthy adults. Randomized controlled trials (RCT) and controlled clinical trials (CCT) were included. Participants in the primary studies were required to be adults (≥ 18 Years) and be in good general health, as defined by the trial authors. Studies were considered for inclusion if participants in the treatment group received either COLD-fX, a proprietary standardized extract of North American ginseng root of oral preparations of other root extracts of *Panax quinquefolius* or *Panax ginseng*. The primary outcome was the incidence of common colds throughout the period. Secondary outcomes included the severity, duration of colds, cold symptoms and adverse events. Five relevant RCTs published in four articles were identified. Only one of the studies (Scaglione *et al.* 1996) investigated the effects of a *Panax ginseng* preparation, the others reported effects of

Panax quinquefolius. Scaglione *et al*. (1996) investigated the preparation G115, an extract of *Panax ginseng* roots, in a 12 weeks RCT with parallel groups of intervention (n=114) and placebo (n=113). Participants aged 48 years (mean), 58% male, received either 2x200 mg of ginseng extract or 2 capsules of placebo per day. The incidence of common colds and influenza, the activity of natural killer cells, specific antibody titres, and adverse events were reported. The study authors concluded that G115 helped improve human immune response and was able to protect against common cold and influenza(see **Fig. 7**). According to the authors of the systematic review the study is of low methodological quality reaching a total Jadad score of 2/5. The reasons were an inadequate description of blinding and randomization. Withdrawals and drop-outs were not described. Therefore data were not sufficient to draw firm conclusions on the efficacy of ginseng extract in prevention of common colds.

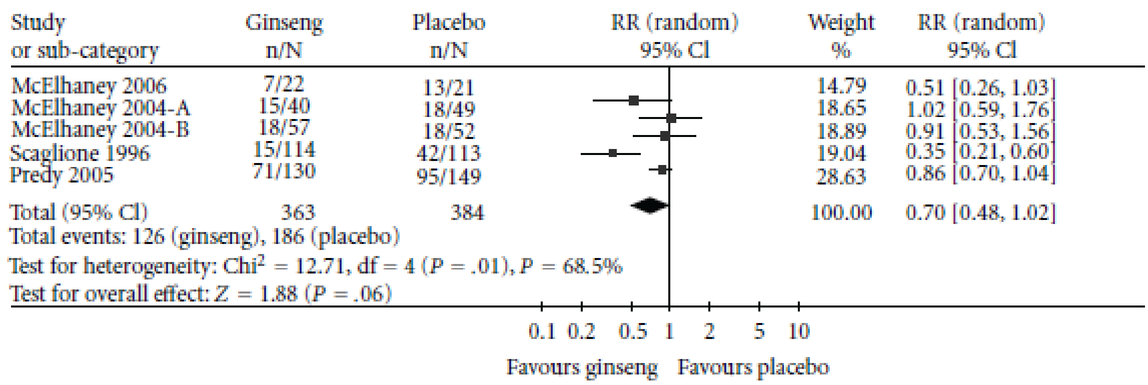


Fig. 7: Forest-plot of incidence of having at least one cold or (in Krebs Seida *et al.* (2011)) acute respiratory infection

Assessor's comment:

Only one of the five included studies refers to a Panax ginseng preparation (G115). The study is of low methodological quality and therefore, no strong evidence on the efficacy of G115 in prevention of common cold can be deduced, even though Scaglione et al. (1996) report a positive outcome.

An *et al*. (2011): Oral ginseng formulae for stable chronic obstructive pulmonary disease: A systematic review

The objective of this systematic review was to evaluate the effectiveness and safety of orally administered Chinese herbal medicines formulae containing ginseng or ginseng extracts. RCTs on stable chronic obstructive pulmonary disease (COPD) patients of all stages, of any age, gender or ethnic origin with or without blinding were considered. Orally administered interventions of ginseng Chinese herbal medicines formulae compared with placebo, no treatment, non-ginseng formulae or pharmacotherapy were examined. Included studies needed to report at least one of the following four primary outcome measurements: spirometric parameters, percentage of effectiveness of symptom changes, quality of life or frequency of COPD exacerbations. Adverse events reported in the included studies were recorded as a secondary outcome measure. Overall, twelve studies met the selection criteria; one of them (Gross *et al.* 2002) evaluated the effects of a *Panax ginseng* monopreparation (G115). According to the reviewers the study of Gross *et al*. (2002) reached a Jadad score of 5/5, whereas the other studies were in general of low methodological quality (Jadad score 1/5 or 2/5). For details see the section on the herbal preparation D (extract G115).

Assessor’s comment:

The systematic review is of limited value in the assessment of the efficacy of Panax ginseng preparations in the treatment of COPD as most of the included studies refer to traditional Chinese herbal medicines formulae consisting Panax ginseng only as minor component. Only one study of good methodological quality investigated a Panax ginseng monopreparation (G 115) and showed a positive outcome. However, the small number of participants (92) limits the conclusiveness and further studies confirming these results have to be conducted. Furthermore, ginseng has not been in medicinal use for the treatment of COPD so far and therefore well-established use cannot be proposed in this indication.

Jang *et al*. (2008): Red ginseng for treating erectile dysfunction: a systematic review

Jang *et al*. (2008) evaluated the evidence for the effectiveness of red ginseng for treating erectile dysfunction (ED). Seven randomized controlled clinical trials [Choi *et al.* (1995, only abstract available), Hong *et al. (*2002, only abstract available), Choi & Choi (2001, no abstract available), Choi *et al.* (2003, no abstract available), Kim & Paick (1999, only abstract available), Choi & Choi (1999, no abstract available), De Andrade *et al.* (2007)], most of them having a low or average methodological quality, met the inclusion criteria. Five of the included trials adopted a two-armed parallel group design, one three-armed parallel group design and one cross-over design. The seven trials evaluated 363 men aged from 24 to 70 years old. The range of duration of ED was from one to 30 years. The duration of treatment reached ranged from 4 to 12 weeks. The adopted doses of red ginseng were 600 mg three times daily in 4 trials, 900 mg in two studies and 1000 mg in one trial. For further details concerning the included trials see **Table 6**.

Table 6

Summary of clinical studies of Korean red ginseng for erectile dysfunction compared with placebo control

Reference	Study design, allocation concealment	Number of patient in study and ED aetiology	Age range (years)	Severity of ED Duration of ED (years)	Dose (mg × 3/days)	Treatment duration (weeks)	Main outcome measures	Results (sample size)	Adverse effect	Jadad score*
Choi *et al.* [6]	Parallel, PB, n.r.	90† Psychogenic ED	25–70	Mild or mild to moderate (1–30)	600	12	Report of improvement of erection and sexual satisfaction by patients and partner (structured interview)	Positive response RG (60) *vs.* placebo (9), $p < 0.05$	(+) None	2 (1 + 1 + 0 + 0 + 0)
Choi & Choi [10]	Parallel, PB, n.r.	50 Psychogenic ED	27–68	Erectile failure: mean IIEF Q3: 2.43 mean IIEF Q4: 1.82 (1–29)	600	8	1) Response to global efficacy question 2) IIEF	1) Positive response RG(14) *vs.* placebo (6) 2) Intergroup difference of score, $P < 0.05$	Gastric upset (RG: 1; P: 1) (+)	1 (1 + 0 + 0 + 0 + 0)
Choi *et al.* [11]	Parallel, PB, n.r.	28 Psychogenic ED	24–68	Erectile failure: mixed (1–29)	600	4	Total IIEF score and global efficacy question	Improvement RG (12) *vs.* placebo (3)	Headache, insomnia (RG:3) (+)	1 (1 + 0 + 0 + 0 + 0)
Kim & Paick [12]	Parallel, PB, n.r.	26 Mild vasculogenic impotence	29–61	Mild ED PSV (20 to 35 cm s^{-1}) (n.r.)	900	12	Watts sexual function questionnaire	Response sample size was not reported Intergroup difference of score, NS Within group (RG: $P = 0.014$)	n.r. (–)	3 (1 + 0 + 1 + 1 + 0)
Choi et al. [13]	Parallel, DB, n.r.	64 Any kind of ED	39–50	Rigidity <70% (mean duration, 1.7 to 4.5)	600	12	Self reported questionnaire related with ED	Improvement RG (18) *vs.* placebo (6)	Constipation: (RG, 2) Gastric upset (RG, 2; P, 3) (+)	1 (1 + 0 + 0 + 0 + 0)
Hong *et al.* [7]	Cross-over, DB, n.r. Assessor blind	45 Any kind of ED	54 (mean)	Inability to archive and maintain erection sufficient for normal sexual satisfaction (n.r.)	900	8	1) Response to global efficacy question (erection) 2) Total IIEF score	1) Improvement RG (27) *vs.* placebo (9) 2) Intergroup difference of score, $P < 0.01$	Gastric upset (RG: 1) (+)	5 (1 + 1 + 1 + 1 + 1)
de Andrade *et al.* [14]	Parallel, DB, n.r.	60 Any kind of ED	26–70	IIEF-5 score: 13–21 (mild or mild to moderate) (n.r.)	1000	12	1) Response to global efficacy question (erection) 2) Total IIEF5	1) Improvement RG (20) *vs.* placebo (0) 2) Intergroup difference of score, $P = 0.00003$	Headache, insomnia (RG:3) (+)	2 (1 + 0 + 0 + 1 + 0)

*Jadad scores were expressed as total score (randomization + appropriate randomization methods + describing withdrawals and dropouts + double-blinding + appropriate double-blinding methods). †This study is a three-arm parallel design with RG ($n = 30$), placebo ($n = 30$), and trazodone group ($n = 30$). To avoid contamination of analysis, we included only RG and placebo groups. DB, double-blind; ED, erectile dysfunction; IIEF, International Index of Erectile Function; n.r., not reported; NS, not significant; RG, red ginseng; PB, patient blind; (+) = mentioned in text; (–) = not mentioned in text.

D.-J. Jang et al.

Six RCTs reported the therapeutic efficacy (improvement of erectile dysfunction) of red ginseng compared with placebo control and all favoured ginseng. The meta analysis of the RCTs suggested red ginseng to be superior to placebo. Subgroup analyses also showed beneficial effects of red ginseng in psychogenic ED. Four RCTs tested the effects of red ginseng for sexual function on questionnaires compared with placebo and all trials reported positive effects of red ginseng. Three trials used the international Index of Erectile Function while one RCT employed Watts sexual function questionnaire. The meta-analysis of these three studies with available data showed an effect in favour of red ginseng on sexual function compared with placebo. For details see **Fig. 8**.

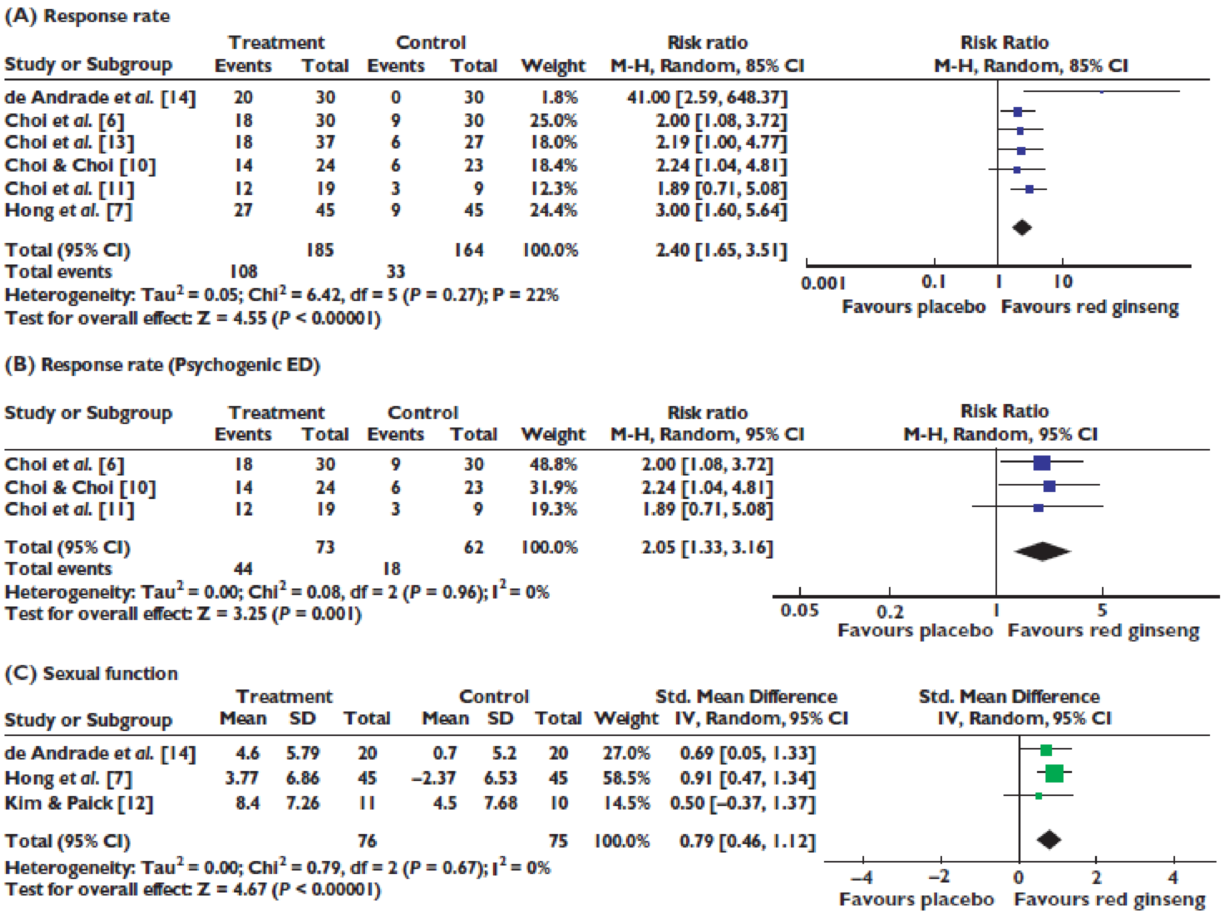


Fig. 8: Forest plot of red ginseng for ED on response effectiveness in all kinds of ED (A), psychogenic ED (B) and on sexual function on questionnaires (C); ED erectile dysfunction; IIEF: International Index of Erectile function

The study results suggested that red ginseng was more effective than placebo in treating erectile dysfunction. However, the number of trials, the total sample size, and the methodological quality of the studies are low. Jang *et al*. (2008) stated that only one RCT (Hong *et al.* 2002, only abstract available) was of good methodological quality. None of the studies reported a power calculation, and sample sizes were very small in some RCT's with two having less than 30 participants. In addition, all included trials seemed to have failed to report details about ethical approval. In some studies non-validated questionnaires were used.

Adverse effects of red ginseng were reported in five of the reviewed RCTs [Hong *et al.* (2002, only abstract available), Choi & Choi (2001, no abstract available), Choi *et al.* (2003, no abstract available), Choi & Choi (1999, no abstract available), De Andrade *et al.* (2007)]. Six cases of headache or insomnia, four cases of gastric upset and two cases of constipation were reported, while tree cases of gastric upset occurred with placebo.

Jang *et al*. (2008) concluded that although the systematic review and the meta-analysis provided suggestive evidence, there were several shortcomings limiting the conclusiveness of this systematic review. The total number of RCTs that were included in this analysis, the total sample size and the average methodological quality of the primary studies was too low to draw firm conclusions.

Assessor's comment:

Jang et al. (2008) report several shortcomings that limit the conclusiveness of the systematic review on the treatment of red ginseng in erectile dysfunction. Jang et al. state, that in all but one cases (Hong et al. 2002, Jadad score 5/5, only abstract available) the methodological quality of the clinical studies was low. This is in contrast to the assessment by Lee & Son (2011), who found the clinical study by Hong et al. (2002)to be also of low methodological quality (Jadad score 2/5). However, the study conducted by Hong et al. (2002) showed a positive outcome but included only a small number of participants having limited statistic power. Therefore, well-established use is not proposed for red ginseng for the indication erectile dysfunction.

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

Numerous clinical studies on ginseng preparations, especially on powdered white (preparation B) and red ginseng (preparation K), and the extract G115 (preparation D) have been conducted since the 1980s. According to the long standing use of ginseng preparations as a "tonic" the spectrum of investigated indications is broad and the studies are very heterogeneous. Applied dosages range from 200 mg per day (extracts) up to 6 g per day (powdered herbal substance). Clinical trials have been conducted on the effects of ginseng preparations on cognitive function, on metabolism, especially blood glucose level and blood lipid level, on cardiovascular function, on erectile dysfunction, on quality of life, vitality and improvement of the immune system and chronic respiratory diseases. In many cases, especially in older studies, the methodological quality showed deficiencies. Systematic reviews have been conducted on general aspects of safety and efficacy of *Panax ginseng* as well as on certain indications such as cognitive function, cardiovascular risk factors, stable chronic obstructive pulmonary disease, prevention of common cold in healthy adults and erectile dysfunction. Some of the included clinical studies indicate beneficial effects (e.g. in some aspects of cognitive function) but due to the heterogeneity of the studies regarding investigated preparations and study design, deficiencies in methodological quality and small numbers of study participants, none of the systematic reviews allows to deduce strong evidence for clinical efficacy in the respective indication. Single studies on well-defined preparations often show contradictory results. Therefore, at the moment, well-established use cannot be proposed for *Panax ginseng* preparations. Nevertheless, many of the preparations which are currently marketed in the European Union fulfil the criteria for traditional use according to Directive 2001/83/EC as amended and the plausibility of traditional use and established posology in the proposed indication is supported by the numerous clinical investigations.

5. Clinical Safety/Pharmacovigilance

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

Coon & Ernst (2002): A systematic review of Adverse Effects and Drug Interactions

In 2002 this systematic review of adverse effects and drug interactions of *Panax ginseng* was conducted in order to evaluate all available safety data on *Panax ginseng* roots and extracts thereof that had been reported in clinical trials. 146 clinical trials were located; of these 82 reported the effects of *Panax ginseng* alone whilst 64 reported the effects of ginseng in a multi-preparation. 48 of the studies on ginseng mono-preparations were placebo controlled, 14 compared the effects of ginseng with that of other compounds and 20 studies had no control group. Study populations included healthy volunteers, athletes, the elderly, patients with erectile dysfunction, postmenopausal women and patients with essential hypertension, with respiratory diseases and with hepatitis. Subjects received ginseng for two to three months in 31 of 82 studies, the longest was 2 years in duration and there were five studies in which ginseng was administered as a single dose. In 25 studies a standardised extract of *Panax ginseng*, G115 (4% ginsenosides) was used at a daily dose of 200 mg. 26 studies used Korean red ginseng powder at doses of between one and 11.25 g/day, two studies involved topical application of a ginseng extract containing 14% ginsenosides, other studies used various forms of ginseng in daily dosages from 100 mg to 6 g, in many cases the preparations were not specified in detail.

No information was provided regarding adverse events experienced during treatment with ginseng in 42 of the studies. In five studies details of adverse events and patient withdrawals due to adverse events were provided but there was no indication as to which treatment the patients were receiving when adverse events were experienced. In 20 studies no adverse events were observed in any patient, whilst in the remaining 15 studies the following adverse events were reported: diarrhoea and gastrointestinal disorders, anxiety, sleep related problems, epigastralgia, flu/cold, headache, contact urticarial reaction, itching, eye burning, improved motor efficiency, feelings of well-being and stimulation, increased appetite, skin eruptions, lighter hand, and skin feeling “too tight”.

A total of 27 case reports following the ingestion of ginseng were identified by the reviewers. The reports referred to cerebral arteritis with explosive headache, nausea, vomiting, and chest tightness, mastalgia, gynaecomastia and vaginal bleeding, diuretic resistance, Stevens-Johnson syndrome, psychological disturbances, hypertension, shortness of breath, dizziness and inability to concentrate, agranulocytosis, and eye symptoms. In 22 of the case reports no information was provided regarding the type or dose of ginseng ingested.

<u>Mastalgia, vaginal bleeding and gynaecomastia:</u>

Six cases of women with mastalgia, two of post-menopausal vaginal bleeding and one of metrorrhagia and one case of gynaecomastia in a man had been described after intake of ginseng powder and extracts. In one case a 72-year-old woman experienced vaginal bleeding after the intake of 200 mg/day of ginseng extract in combination with minerals and vitamins (Greenspan 1983). In another case a 48-year-old woman was admitted to hospital with a 3-week history of methrorrhagia after intake of 120 mg/day (recommended dose 40 to 80 mg/day) (Palop-Larrea *et al.* 2000). A 44-year-old postmenopausal woman reported vaginal bleeding after using a ginseng face cream (Hopkins *et al.* 1988, only abstract available). A 42-year-old man was found to have chest pain and a tumour like swelling 8x6 cm in size in his right breast after taking a combination of 240 mg/day ginseng, minerals and vitamins for 3 months (Palop *et al.* 1999, only abstract available). In most cases the symptoms resolved within few days after cessation of the ginseng preparations.

<u>Diuretic resistance:</u>

A 63-year-old man experienced diuretic resistance 10 days after daily ingestion of 10 to 12 tablets of a germanium-containing ginseng-preparation. Following cessation of the tablets the symptoms improved and after re-challenge they returned. The authors concluded that the problem was more likely to be caused by the germanium than the ginseng (Becker *et al.* 1996)

<u>Stevens-Johnson Syndrome:</u>

A 27-year old man experienced typical Stevens-Johnson syndrome (bilateral conjunctivitis, dry cough, a macular rash on his face, painful erosions on his mouth and urogenital mucosa, corneal ulceration and widespread purpuric macules) three days after taking two ginseng tablets a day for three days

(Dega *et al.* 1996). The patient was a regular ginseng user and had not taken any other medication the week before the onset of symptoms. The authors indicated that the ginseng preparation might have been contaminated; the sample was not chemically analysed.

<u>Psychiatric conditions:</u>

A 35-year old woman with depressive illness who maintained on lithium carbonate and amitriptyline experienced a manic episode requiring hospital admission 10 days after interrupting her therapy and starting treatment with one tablet of ginseng a day. Her symptoms improved following cessation of ginseng and a return to her previous medication (González-Seijo *et al.* 1995, no abstract available). The reviewers stated that it was debatable whether the symptoms were not, at least in part, caused by the cessation of lithium. Five in-patients with diagnoses of schizophrenia were observed to become generally irritable, uncooperative with their treatment programmes and overactive with disturbed sleep after smoking ginseng-containing cigarettes. After having stopped smoking these cigarettes their behaviour was seen to improve (Wilkie & Cordess 1994, only abstract available)

<u>Cerebral arteritis:</u>

A 28-year-old-woman was admitted to hospital with severe headache 6 days after ingesting a bowl of extract (approximately 200 ml) made from 60 slices of ginseng root (approximately 25 g dry weight) that was stewed with 400 ml rice wine (22% alcohol). Eight hours after drinking the extract she developed explosive headache, nausea and vomiting and chest tightness. Cerebral angiograms demonstrated appearances consistent with cerebral arteritis. The headache gradually resolved over the next 10 days. The authors concluded that the close temporal association between ginseng intake and the onset of symptoms suggested a causal relationship (Ryu & Chien 1995, only abstract available)

<u>Agranulocytosis:</u>

Four non-Chinese patients developed life-threatening agranulocytosis while taking Chinese herbal medicines for relief of arthritis and back pain. Subsequent analysis of the herbal preparations revealed the presence of undeclared aminopyrine and phenylbutazone, both of which are known to cause agranulocytosis. The authors concluded that these contaminants were responsible for the observed symptoms in these patients (Ries *et al.* 1975, only abstract available)

<u>Eye symptoms:</u>

Two cases of ginseng poisoning associated with mydriasis and disturbance in accommodation with dizziness and semi-consciousness have been reported (Lou *et al.* 1989, only abstract available).

<u>Hypertension:</u>

A young man presented to his doctor with hypertension, shortness of breath, dizziness and inability to concentrate. He had been taking ginseng supplements for three years. Following cessation of the ginseng supplements his symptoms improved and did not recur (Hammond & Whitworth 1981, no abstract available). A female patient with hypertension, who was receiving no other medication reported an increase in her blood pressure from between 160/90 and 240/110 to 280/120 mm Hg following treatment with ginseng for a few days (Nielsen 1988, no abstract available). Three to 4 days after cessation of the ginseng product her blood pressure had fallen to 240/110 mm Hg and treatment with a β-blocker was commenced.

<u>Epidemiological studies:</u>

Three case control studies of cancer in Korea in over 10000 patients did not provide any information regarding adverse events. A further case control study in patients with oligoasthenospermia did not contain details of any adverse effects experienced during the trial. A retrospective cohort study of 1800 elderly patients taking a combination product containing vitamins, minerals and a standardised ginseng extract (G115) reported the following adverse events: epigastric disorders, hypertension, muscular pain and erythema. The authors reported no clear relationship with the treatment for any of the reported adverse events. An investigation of 133 long-term ginseng users who had been taking ginseng regularly for at least 1 month and were then followed for 2 years described the following symptoms: morning diarrhoea, skin eruptions, demulcent effects on the throat, sleeplessness nervousness, hypertension, euphoria, oedema, decreased appetite, depression, hypotension, and amenorrhoea. High doses (15 g/day) resulted in depersonalisation and confusion in four patients and depression was reported with doses above 15 g/day. The authors also defined a “ginseng abuse syndrome” characterised as hypertension together with nervousness, sleeplessness, skin eruptions, and morning diarrhoea which was reported by 14 of the patients. Participants took a wide variety of commercial ginseng preparations including roots, capsules, tablets, teas, extracts, cigarettes, chewing gum, and candies and these contained a variety of types of ginseng including *Panax ginseng*, *Panax quinquefolius*, Siberian ginseng (*Eleutherococcus senticosus*) and desert ginseng (*Rumex hymenosepalus*) (Siegel 1979). Dosages and administration methods also varied (Siegel 1979).

Spontaneous Reporting Schemes (WHO, US FDA, UK Medicines Control Agency, BfArM)

Until May 2001, reports detailing 378 adverse events had been received from the national drug safety bodies of 18 countries; 168 of these related to ginseng monopreparations, 169 to ginseng in combination with other substances. The WHO cautioned that the information from their database was not homogenous at least with respect to origin of likelihood that the pharmaceutical product caused the adverse reaction and that the information did not represent the opinion of the WHO. Additional information was available for 178 of these reactions from 86 individual patients. Forty-three of these reports related to ginseng-monopreparations and 43 to ginseng in combination with other substances. In 25 cases related to ginseng-monopreparations ginseng was the only suspected drug although one patient was taking other medication concomitantly. The adverse event was described as a drug interaction in two cases (ginseng +vitamin B complex +sertraline, ginseng + warfarin). In eleven cases a definite improvement was seen following cessation of ginseng; two cases showed no improvement and in 30 cases this information was not provided. Rechallenge led to recurrence of symptoms. No information regarding causality was provided in 24 cases, but relationship was believed to be possible in 14 cases, probable in four cases and certain in two cases. 21 patients recovered without sequelae, two had not yet recovered and in the remaining 20 patients the outcome was unknown.

An update in October 1998 of the web report of the Special Nutritionals Adverse Event Monitoring System (voluntary scheme, FDA) included 117 case reports associated with products containing ginseng or *Panax ginseng*. In all but 19 cases the products involved were combination preparations of which *Panax ginseng* was listed as one of a large number of ingredients. Ten patients reported 19 adverse events in which ginseng was the only suspected drug, the remaining nine reports include ginseng as one of up to nine other suspected herbal medications. No information regarding outcomes or causality was available.

Between July 1963 and May 2001, the UK MCA had received reports of adverse events with *Panax ginseng* for 17 patients with no fatal outcomes. These patients had reported 36 adverse reactions, 31 after ingestion of ginseng alone and five following a combination product. Two drug interactions were reported with a ginseng monopreparation; however, no further details were provided and no information regarding outcomes or causality for any of the adverse events was available.

A total of 15 case reports for *Panax ginseng* had been received by the BfArM prior to May 2001, two of these for ginseng monopreparations (abdominal pain and increase in prothrombin). Amongst the adverse reactions reported for ginseng combination products there were seven gastrointestinal problems, four liver related disorders, myalgia, herpes zoster, face oedema, circulatory failure, anaphylactoid reaction, eye pain, hallucination, dyskinesia, and hyperkinesia. No further information was provided.

<u>Data from Ginseng manufacturers</u>

Information was received from two of the 12 manufacturers/distributors of ginseng products contacted. For one product containing extract G115 (herbal preparation D in the monograph) the manufacturer had received an unspecified number of reports regarding adverse events experienced by patients for G115 (herbal preparation D) that included problems of a psychiatric and gastrointestinal nature, disorders of the central and peripheral nervous system, reproductive system, respiratory cardiovascular system, urinary system, and musculoskeletal system. There were also several heart rate and rhythm disorders, platelet, bleeding and clotting disorders, skin reactions and disorders of the body as a whole. Coon *et al*. stated that insufficient information was available to comment on causality. The manufacturer had also received an unspecified number of case reports of adverse events for a combination product (G115 + minerals and vitamins). Of these several were considered serious. None of the adverse events was fatal and after careful consideration of the circumstances surrounding each event was not believed to be a causal factor in any case. Another company had received one medically unconfirmed report of a dermatological reaction (skin eruption) which occurred during treatment with ginseng root powder. The patient was also receiving treatment with fenofibrate, glibenclamide (glyburide) and naftidrofuryl. A later rechallenge with naftidrofuryl was without adverse event. Causality was rated as plausible for ginseng, glibenclamide and fenofibrate.

Coon & Ernst (2002) stated that in general the establishment of a causal relationship between the ingestion/application of a herbal product and a subsequent adverse event is difficult. There are additional difficulties with herbal products due to the potential for contamination, adulteration and mislabelling. The bulk of the data presented should be evaluated with caution. Information from clinical trials was also difficult to interpret since trials designed to assess efficacy rarely collected rigorous information in the report, in case of this systematic review 50% of trials did not provide such information. This review identified 146 clinical trials which represented the exposure of over 8500 individuals to ginseng preparations (over 3500 to monopreparations) with relatively few adverse events being reported. The most frequent of these were gastrointestinal or sleep related in nature with few precipitating withdrawal of the patient from the study and no apparent differences between the ginseng and control groups. The data obtained from spontaneous reporting schemes was often insufficient thus not allowing conclusive attribution of causality. Collation of the available data for mono-preparations suggested that adverse events were on the whole mild and reversible although serious events had occurred. Interpretation of the data regarding ginseng in combination with other ingredients was more difficult as many of the constituents within combination products had recognised adverse effects themselves. The authors concluded that the available data suggested that *Panax ginseng* was well tolerated by most users, with the most frequently experienced adverse effects being mild and reversible. Ginseng combination products were associated with more adverse events, presumably due to the other ingredients.

5.2. Patient exposure

Coon & Ernst (2002) reviewed 146 clinical trials representing an exposure of over 8500 individuals to ginseng preparations (3500 thereof were given *Panax ginseng* monopreparations). On the basis of the longstanding worldwide use of *Panax ginseng* a significant exposure can be expected.

5.3. Adverse events and serious adverse events and deaths

See 5.1.

In general, serious adverse events and deaths with a clear causal relationship have not been reported after ginseng intake so far. Most reported adverse events from clinical studies or spontaneous reporting schemes were mild and reversible. The most frequent adverse events reported from clinical studies were gastrointestinal or sleep related, including stomach discomfort, nausea, vomiting, epigastralgia, diarrhoea, constipation, headache, and insomnia. Furthermore hypersensitivity reactions like urticaria and itching as well as eye burning have been reported. Three case reports on allergic reactions related to ginseng (Lee JY *et al.* 2006, Kim KM *et al.* 2008, Lee *et al.* 2012) and one publication evaluating hypersensitivity reactions in plants of the Araliaceae family (Oka *et al.* 1999) are briefly discussed in the following section.

Lee JY *et al.* (2006)

The authors reported a 29-year-old female patient that presented to the emergency department of Eulji University Hospital in Daejeon, Korea, for the treatment of dyspnea, wheezing and cough. The patient had been incidentally exposed to airborne Sanyak (*Dioscorea batatas*) dust, during the process of grinding dried Sanyak into powder, five minutes before the onset of symptoms. She had been a merchant of herbal materials for the previous 26 months. Twelve months before her visit, she had been admitted to another hospital and diagnosed with bronchial asthma after the sudden onset of dyspnea following an exposure to airborne ginseng dust. The patient had been suffering from nasal itching, sneezing, rhinorrhea and nasal obstruction during the spring season for 6 years and had also experienced itching and swelling of the lips, tongue, and throat after ingesting fresh chestnut, sweet potato, and ginseng. Proteins were extracted from Ginseng and Sanyak (no information on extraction procedure provided) and used for skin-prick tests, inhalation challenge tests, and laboratory studies. The ginseng extract showed a positive bronchial provocation and positive responses to the skin-prick test but IgE and IgG4 antibodies specific to ginseng extract could not be determined by immunoblotting and ELISA inhibition tests in this study.

Kim KM *et al.* (2008)

The authors reported a 34-year-old woman that presented with abdominal pain and diarrhea after eating many different foods and experienced generalized urticarial and angioedema after eating persimmon. Five years previously, she had started working at a Korean ginseng wholesale premise, where she was exposed to dried ginseng and ginseng dust. After starting the work, she developed frequent rhinorrhea, sneezing, and nasal obstruction. Six months previously, she had developed dyspnea and wheezing on a daily basis, and these symptoms were aggravated at work, but improved after a weekend break. She had no allergic symptoms after ingestion of non-dried ginseng or steamed red ginseng. A ginseng-extract was prepared as follows: the comminuted drug was extracted with phosphate-buffered saline, pH 7.5, drug:extraction-solvent ratio of 1:5 at 4°C for 24 h; after centrifugation the supernatant was dialyzed applying a molecular weight cut-off of 6kDa. The extract was used for skin prick tests and specific bronchial challenge tests. Skin prick testing with a 1:100 dilution of the ginseng extract induced a strong positive response. An allergen bronchial provocation test with a 1:100 dilution of the extract induced no asthmatic reaction but an early asthmatic reaction with severe coughing and dyspnea was observed 5 min after inhalation of a 1:10 dilution of the extract. A physical examination revealed expiratory wheezing throughout the lung field and FEV1 was significantly reduced versus baseline. Serum specific IgE levels to ginseng extract were significantly elevated and ELISA inhibition tests showed dose-dependent inhibition by ginseng extract. Immunoblot analysis revealed four specific IgE binding components at 26, 30, 47, and 60 kDa.

Lee *et al.* (2012)

Lee *et al*. (2012) reported a 44-year-olf man who experienced rhinorrhea and nasal stiffness, followed by respiratory difficulty with wheeze and abdominal pain 10 minutes after oral intake of fresh Korean ginseng. He had suffered from episodes of allergic rhinitis during the spring season for several years.

The skin prick test showed positive responses to alder, birch pollens, fresh ginseng and ginseng extracts (1:500 w/v, no further information). The methacholine bronchial challenge test produced a positive result at 5.83 mg/ml. The open oral challenge was performed using 50 g of fresh ginseng and the patient showed immediate onset of facial flushing, cough, respiratory difficulty with wheeze and abdominal pain. Serum specific IGE and IgG4 were not detected but a higher level of serum-specific IgG1 was noted in the patient samples as compared to the control samples. Basophil activation test showed a dose-dependent increase in the expression of CD203c and CD63 on the basophils of the patient in response to ginseng extracts, while no changes were observed in the controls. The authors stated that in contrast to the previously reported case (Kim KM *et al.* 2008) the allergic reaction after oral exposure to ginseng was mediated by non-IgE dependent direct activation of basophil/mast cells and further investigations on the mechanism is suggested.

Oka *et al.* (1999)

Analogues of falcarinol (=panaxynol), a compound which is also present in *Panax ginseng*, have been identified as strong sensitizers in *Dendropanax trifidus*, *Fatsia japonica*, *Schefflera arboricola* and other species of the Araliaceae family. One of the purposes of this study was to investigate the cross-reacting of these allergens with other plants in the Araliaceae family e.g. *Hedera helix* and *Panax ginseng*. Five volunteers with known hypersensitivity to *Dendropanax trifidus* were subjected to patch testing with fractions and isolated compounds of *Dendropanax trifidus* as well as extracts of *Hedera helix*, *Schefflera arboricola*, and *Panax ginseng* (ethanol extract of *Panax ginseng* root powder, 1%; no further information). One person showed at positive reaction to the extract of *Panax ginseng*. Furthermore 10 healthy subjects with no history of contact dermatitis due to these plants were patch tested with the leaves of *Hedera helix*, *Schefflera arboricola* and the ethanolic extract of *Panax ginseng* root. None of the subjects showed a positive reaction to *Panax ginseng*.

Assessor's comment:

The polyacetylene falcarinol (panaxynol) and its analogues are present in several members of the closely related plant families of the Apiaceae (e.g. Daucus carota, Apium graveolens, Petroselinum hortense, Pastinaca sativa) and Araliaceae (e.g. Hedera helix, Schefflera arboricola, Panax ginseng). Falcarinol is a strong irritant and has been identified in H. helix as one of the compounds with moderate allergenic potential and for this plant a number of reports on allergic contact dermatitis have been published (Paulsen et al. 2010). Most cases were occupational (e.g. gardeners) after skin contact with fresh ivy leaves, which contained >1% falcarinol. For Panax ginseng only two case reports on allergic reactions after exposure to airborne ginseng dust and one case after oral ingestion of the fresh root have been described. Since available data on the sensitizing potential of Panax ginseng preparations after oral application and the possibility of allergic "cross-reactions" to other plants of the Araliaceae family are scarce (only one case report), for section 4.3 of the monograph the following wording is proposed: Hypersensitivity to the active substance.

5.4. Laboratory findings

Not applicable.

5.5. Safety in special populations and situations

Drug abuse

Siegel (1979), Siegel (1980)

133 subjects which had been using "ginseng" regularly for at least one month before recruitment were evaluated. After an initial interview and drug-history questionnaire, subjects were given physical and

psychological examinations. These examinations were repeated at six-month intervals for two years. A wide variety of commercial “ginseng” preparations, including roots, capsules, tablets, teas, extracts, cigarettes, chewing gum and candies was used. Most preparations were applied orally, but a small number of persons experimented with intranasal or injection routes. Several users also employed ginseng topically in the form of cosmetic creams and oils. Ginseng dosages varied with preparations (up to 10 g three times a day), but generally, subjects used them for three to seven days per week. In the study report a “Ginseng Abuse Syndrome” (GAS) is described for 14 subjects employing up to 15 g *Panax ginseng* roots per day orally in combination with caffeinated beverages. The syndrome is defined as hypertension together with nervousness, sleeplessness, skin eruptions, edema, and morning diarrhea. Symptoms were reversible, when the daily dose was reduced to an average of 1.7 g. One user reported that abrupt withdrawal precipitated hypotension, weakness and tremor. Ten GAS subjects became euphoric, restless, agitated, and insomniac. Doses of 15 g resulted in feelings of depersonalization and confusion for four subjects, depression was reported following doses higher than 15 g for 24 weeks by six subjects.

Assessor’s comment:

The study by Siegel (1979) has to be interpreted with caution. First of all, preparations were not clearly defined including not only Panax ginseng but also Panax quinquefolius, Eleutherococcus senticosus, and Rumex hymenosepalus. Extracts, without any characterization regarding extraction solvent, DER or phytochemical profile, as well as the crude drug were applied orally, but in some cases also intranasal or by injection. Subjects who used Panax ginseng root material and experienced the GAS reached daily doses up to 15 g which is far higher than the commonly recommended dose of up to 6 g of powdered drug per day. All of the 14 persons reporting GAS consumed caffeine beverages concomitantly. Therefore it remains questionable whether the symptoms of CNS excitation can be related only to the (mis)-use of ginseng. Finally, symptoms such as hypertension or depression have been reported after long-term use of “ginseng” (13 and 24 weeks). The effects concerning blood pressure are contradictory. Siegel (1979) describes substantial effects in 14 persons, who had normal ranges of blood pressure at the beginning of the study and elevated values following ginseng use. In contrast, five other subjects showed lowered blood pressure, although the effect was not statistically significant. However, there is no study protocol describing the examination of blood-pressure in detail. Although such effects have been reported only for higher doses and long-term use it is suggested to limit the duration of use of ginseng preparations to 12 weeks.

Impact on CYP 450 - Drug interactions

<u>Anderson *et al.* (2003)</u>

20 healthy male (age 28±7 years) and female (age 36±9 years) volunteers received 100 mg of the ginseng extract G115 twice daily for 2 weeks. The urinary excretion of the 6-beta-hydroxycortisol / cortisol ratio was used as marker of CYP 3A enzyme induction. No enzyme induction could be found.

<u>Gurley *et al.* (2005, abstract only)</u>

Twelve healthy volunteers (age between 60 and 76 years) received *Panax ginseng* (no further description in the abstract) for 28 days. Probe drug cocktails of midazolam, caffeine, chloroxazone and debrisoquine were administered before and at the end of supplementation. Pre- and post-supplementation phenotypic ratios were determined for CYP3A4, CYP1A2, CYP2E1, and CYP2D6 using 1-hydroxymidazolam/midazolam serum ratios (1-hour), paraxanthine/caffeine serum ratios (6-hour), 6-hydroxychloroxazone/chloroxazone serum ratios (2-hour), and debrisoquine urinary recovery ratios (8-hour), respectively. *Panax ginseng* showed a statistically significant inhibition of CYP2D6 but the magnitude of the effect (~7%) did not appear to be clinically relevant. CYP1A2 was not affected.

Coon & Ernst (2002)

In the systematic review on "Adverse effects and drug interactions" Coon & Ernst (2002) integrated 4 reports concerning possible herb-drug interactions with phenelzine, warfarin, and alcohol. A 64-year-old woman described symptoms of headache and tremulousness when a product containing ginseng was added to her therapy of phenelzine. Three years later, whilst still taking phenelzine she experienced similar symptoms on ingesting ginseng capsules (Shader & Greenblatt 1985, Shader & Greenblatt 1988).

A 43-year-old woman who had had a long standing depressive illness and whose medication included phenelzine, triazolam and lorazepam experienced an improvement of her depression which escalated into maniac like symptoms while taking a combination of ginseng and bee pollen. When the ginseng preparation was discontinued she no longer benefited from any therapeutic effect from phenelzine (Jones & Runikis 1987).

A 47-year-old man receiving warfarin started taking three capsules a day of a standardized ginseng extract (G115). His Interational Normalised Ratio (INR) which had been stable for the previous 9 months declined to 1.5 two weeks after commencing ginseng supplementation but returned to within the target range on cessation of the ginseng capsules. The interaction had been rated as probable by the authors; however a clear resolution of the case report was given (Janetsky 1997). A subsequent assessment in a rat model showed no significant impact of ginseng on the pharmacodynamics or pharmacokinetics of warfarin (Zhu *et al.* 1999, only abstract available)

An open, non-randomised clinical trial of 14 healthy volunteers suggested that *Panax ginseng* could enhance the blood alcohol clearance rate. Forty minutes after the administration of alcohol and ginseng the blood alcohol level was 30% lower than following alcohol ingestion alone (Lee *et al.* 1987).

Jiang *et al.* (2004), Jiang *et al.* (2006)

Jiang *et al*. (2004, 2006) investigated the effect of St. John's wort extract and a Korean red ginseng extract (equivalent to 0.5 g *Panax ginseng* root and 8.93 mg ginsenosides as ginsenoside Rg_1 per capsule) on the pharmacokinetics and pharmacodynamics of warfarin. In an open-label, three-way crossover randomized study 12 healthy male subjects received a single 25 mg dose of warfarin alone or after 7 days pretreatment with ginseng. Dosing of ginseng was continued for 7 days after administration of warfarin. Platelet aggregation, international normalized ratio of prothrombin time, warfarin enantiomer protein binding, warfarin enantiomer concentrations in plasma and S-7-hydroxywarfarin concentration in urine were measured. The urine excretion rate of S-7-hydroxywarfarin was reduced by treatment with ginseng but the effect was not clinically significant. Other pharmacokinetic and pharmacodynamic parameters of warfarin were not affected.

Lee SH *et al.* (2008)

The study investigated the interaction between warfarin and an aqueous extract of *Panax ginseng* (DER 11:1, extraction time 4h at 100°C) by observing the prothrombin time (PT) and the international normalized ratio (INR) in ischemic stroke patients who did not have a history of taking warfarin. 25 patients newly diagnosed with ischemic stroke by brain computed tomography or magnetic resonance imaging were randomized into 2 groups. One group received *Panax ginseng* extract and warfarin and the control group received only warfarin for 2 weeks. The warfarin dose was restricted to 2 mg in the first week and 5 mg in the second week. The peak values and the INR and PT areas under the curve (AUC) in both groups significantly increased compared to those at baseline. However, there was no statistically significant difference in peak values and INR and PT AUC between both groups in both, the first and second weeks. The authors concluded that the administration of this aqueous *Panax ginseng* extract at 1.5 g per day did not interact with warfarin in ischemic stroke patients with normal liver and kidney function.

Lee *et al.* (2010)

The objective of the prospective, randomized, double-blind, crossover study was to determine whether an interaction exists between warfarin and Korean red ginseng. 31 patients with cardiac valve replacement under warfarin therapy and stable INR were included. One group initially received warfarin with 1 g of Korean red ginseng extract for 6 weeks and then after a 3-week washout period received warfarin and placebo. The alternative group received treatment in the opposite order. Blood samples were collected to measure INR and plasma warfarin levels. The primary outcome was the change of INR at 3 and 6 weeks. The secondary outcome was the correlation between INR and warfarin concentrations or weekly doses. There were no statistically significant differences in mean INR change. Furthermore, Korean red ginseng extract did not enhance the anticoagulation effect.

Yuan *et al.* (2004)

This randomized clinical trial describes interactions between the intake of American ginseng (*Panax quinquefolius*) and warfarin. 20 healthy patients received warfarin (5 mg oral daily) for 3 days during week 1 and week 4. Beginning in week 2 patients received either placebo or American ginseng (1.0 g powdered herbal substance). The ginsenoside content was Rb_1 1.93%, Rb_2 0.20%, Rc 0.61% Rd 0.42%, Re 1.68% and Rg_1 0.35%. The peak INR (International Normalized Ratio as parameter for the blood coagulation) decreased in the mean after 2 weeks of administration of American ginseng significantly compared to placebo (-0.19). The INR AUC, peak plasma warfarin level and warfarin AUC were also statistically significantly reduced compared to placebo.

Assessor's comment:

The trial should be considered as preliminary as the number of participants is limited and the data on the individual level are obviously very heterogenuos, although showing some tendencies. The relevance of these findings for the medicinal use of Panax ginseng is not clear. It is evident that the composition of the ginsenosides differs considerably.

Haefeli & Carls 2014

The authors reviewed the current knowledge regarding interactions between herbal medicines and oncological treatment. For ginseng (including also data referring to American ginseng, e.g the above mentioned study by Yuan *et al.* 2004) the authors concluded that there is a low risk for CYP-dependent clinically relevant interactions. However, they stated that a more intense INR monitoring in the first weeks after start or discontinuation of a combination ginseng + warfarin could be advisable.

Assessor's comment on the impact on CYP 450 and drug interactions:

The causality between ginseng intake and possible interactions with phenelzine and warfarin described in the systematic review by Coon & Ernst (2002) is doubtful. Phenelzine is a non-selective MAO-inhibitor known for a broad spectrum of side effects including those mentioned in the case reports. Furthermore, the "ginseng" preparations are not clearly characterized and did not only contain "ginseng" but also other substances. One case report describes a probable interaction of G115 with warfarin but a clear resolution has not been given e.g. it is not excluded that other pharmaceuticals have been used concomitantly.The clinical trial by Yuan et al. (2004) was conducted with preparations of Panax quinquefolius and has to be interpreted with caution concerning the relevance for the medicinal use of Panax ginseng. An assessment in a rat model showed no significant impact of Panax ginseng on the pharmacodynamics or pharmacokinetics of warfarin. Studies in healthy subjects showed no clinically relevant impact of Panax ginseng preparations on the pharmacokinetic and *pharmacodynamic parameters of warfarin. Additionally, the study by Lee et al. (2010) showed that the impact of red ginseng on the INR of patients under warfarin therapy is not statistically significant. Another study which investigated the interaction potential of a Panax ginseng aqueous extract with warfarin showed similar results. Even though the number of patients in both studies (31 and 25 patients, respectively) was rather small the interaction potential of Panax ginseng preparations with warfarin seems to be of minor relevance. This interpretation is endorsed by studies in human volunteers which investigated the influence of Panax ginseng preparations on the CYP 450 showing no clinically relevant impact on CYP3A, CYP1A2 and CYP2D6.*

Use of *Panax ginseng* during pregnancy and lactation

Seely *et al.* (2008)

Seely *et al*. (2008) conducted a systematic review on the safety and efficacy for *Panax ginseng* during pregnancy and lactation. Data on non-estrogenic/estrogenic activity, treatment of intrauterine growth retardation, androgenization, protection of neonatal brain against ethanol damage, teratogenicity, activation of DNA polymerase delta in placenta, and traditional use during pregnancy was evaluated.

A randomized controlled trial of 384 women receiving either ginseng extract or placebo for 16 weeks showed that the beneficial effects in the treatment of menopause are most likely not mediated by hormone replacement-like effects (Wiklund *et al.* 1999, see section 4.2.2). On the other hand, there are case reports and *in vitro* studies including postmenopausal vaginal bleeding, increased serum ceruloplasmin oxidase activity and phytoestrogenic actions of ginsenoside Rb1 (Palmer *et al.* 1978; Hopkins *et al.* 1988, only abstract available; Greenspan 1983, Punnonen & Lukola 1980, Lee YJ *et al.* 2003). A study (Zhang *et al.* 1994, only abstract available) on pregnant women with intrauterine growth retardation did not report any adverse effects associated with ginseng supplementation. A case report of a 30-year-old woman who gave birth to a baby boy with signs of androgenization following ingestion of “ginseng” during her pregnancy (Koren *et al.* 1990) finally revealed that the herbal preparation used was declared as “Siberian ginseng” and adulterated by the herb silk vine (*Periploca sepium*). A study in rats (Okamura *et al.* 1994) reported that ginseng extract prevented an ethanol-induced reduction of neonatal brain weight. The ginsenosides Rg_1, Rb_2, Rd, Rf, and Re were shown to stimulate a potent recovery of cerebellum growth. Studies on isolated ginsenosides Rb_1, Rc, and Re revealed direct teratogenic effects in a model of cultured rat embryos (Chan *et al.* 2003, Chan *et al.* 2004) at concentrations of 30-50 µg/ml. These studies were confirmed by the investigations by Liu *et al*. (2005, 2006) who found embryotoxicity when rat and mice whole embryo cultures were exposed to similar concentrations of the ginsenosides Rg_1 and Rb_1. In lower concentrations the observed effects were not significant compared to the untreated control according to the authors. On the other hand, Lee SR *et al*. (2008) did not detect negative effects of ginsenosides Rb_1, Rg_1, and Re on developmental parameters in the same model at concentrations of 5, 50, and 100 µg/ml. Ginsenosides were found to activate DNA polymerase delta in bovine placenta (Cho *et al.* 1995). Wong (1979, only abstract available) conducted a review of herbs used during pregnancy in Singapore showing that *Panax ginseng* was used in various combinations and various amounts in herbal prescriptions during pregnancy. The author noted that the “active principles” could cross the placenta and reach the fetus but did not discuss if *Panax ginseng* was safe or contraindicated during pregnancy. Two research groups (Hu *et al.* 1995, Hu *et al.* 2001, Concha *et al*. 1996) investigated the effect of *Panax ginseng* on lactating cows and did not report any adverse effects.

Assessor’s comment:

There are no systematic investigations or clinical trials which report the use of ginseng during pregnancy and lactation. Taking into account observations from traditional use of Panax ginseng *preparations there is no strong evidence that the use could be unsafe in pregnancy and lactation. Having a closer look on some case-reports that claim an estrogenic activity, it becomes apparent that causality between the observed effects and the use of Panax ginseng preparations cannot be clearly established. Experiments in animals and in vitro data show contradictory findings concerning teratogenic effects of isolated ginsenosides. Investigations were conducted in a model of cultured rodent embryos applying up to 100 µg/ml of isolated ginsenosides. Considering the current state of knowledge on the pharmacokinetics of ginsenosides such concentrations are not expected to be reached by the consumption of the herbal substance or extracts thereof in recommended doses. Moreover, it is not clear whether ginsenosides could be able to cross the placenta. However, due to a lack of adequate data the use of Panax ginseng preparations is not recommended during pregnancy and lactation.*

5.6. Overall conclusions on clinical safety

Panax ginseng preparations have been used worldwide for many years and so far, no serious adverse events have been reported from clinical trials, epidemiological studies and spontaneous reporting schemes that can be clearly correlated with the ingestion of *Panax ginseng*. Reported adverse effects from clinical trials are mild and mainly gastrointestinal or sleep related, including stomach discomfort, nausea, vomiting, epigastralgia, diarrhoea, constipation, headache, and insomnia. Furthermore hypersensitivity reactions like urticaria and itching as well as eye burning have been reported. A "Ginseng Abuse Syndrome" has been described in literature, defined as hypertension together with nervousness, sleeplessness, skin eruptions, edema and morning diarrhoea after long-term use of daily doses of up to 15 g of "ginseng (-preparations)". However, the used preparations were not clearly defined and included also *Panax quinquefolius*, *Eleutherococcus senticosus* and *Rumex hymenosepalus*. Furthermore, the preparations were not only used orally but also intranasal or by injection and all of the persons reporting the syndrome consumed caffeinated beverages concomitantly. Due to the questionable causality and with regard to the limited recommended daily dose of 6 g and duration of use for not longer than three months, these findings are not regarded to be relevant for safety considerations. Few case reports described possible interactions of *Panax ginseng* preparations with phenelezine and warfarin. These findings were not verified by clinical studies in healthy subjects and patients under warfarin therapy. Furthermore an assessment in a rat model showed no significant impact of *Panax ginseng* on the pharmacodynamics or pharmacokinetic properties of warfarin. Studies in healthy human volunteers showed no clinically relevant impact on CYP3A, CYP1A2 and CYP2D6. No systematic investigations or clinical trials have been established for the use of *Panax ginseng* during pregnancy and lactation. Due to the lack of adequate data the use of *Panax ginseng* preparations is not recommended in pregnancy and lactation.

6. Overall conclusions

The underground parts of *Panax ginseng* C.A. Meyer and herbal preparations thereof have been used worldwide for centuries, especially in traditional medicine systems of Eastern Asia. Various herbal preparations *of Panax ginseng* have been marketed in the European Union for at least 30 years and are used as a "tonic in case of tiredness, weakness, and decreased mental and physical capacity as well as to improve concentration and to improve the general condition during convalescence". With respect to the multiple but mostly non-specific pharmacological actions that have been investigated in preclinical and clinical studies *Panax ginseng* shows similarities to *Eleutherococcus senticosus* [see Community Monograph and Assessment Report on *Eleutherococcus senticosus*].

Despite the fact that numerous clinical studies investigating the pharmacological properties of *Panax ginseng* have been conducted since the 1980s, several systematic reviews reveal that data is still inconclusive and strong evidence for clinical efficacy cannot be deduced. Thus, at the moment, well-established use is not proposed for *Panax ginseng* preparations. Nevertheless, twelve herbal preparations (A-L, see 2.1) of white and red ginseng fulfil the criteria for traditional use according to Directive 2001/83/EC as amended. The posology for each herbal preparation has been established on the basis of literature data and data on authorized or registered herbal medicinal products of *Panax ginseng* provided by EU member states (see 2.1 and 2.3). The plausibility of traditional use and the posology in the proposed indication are supported by the long-standing use and the outcome of numerous preclinical and clinical investigations.

Therefore, in analogy to *E. senticosus* the indication for *Panax ginseng* preparations should be worded as following: Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness. The duration of use is possible up to three months.

Due to the long-standing worldwide use of *Panax ginseng* preparations and the outcome of clinical trials no special safety concerns arise. Adverse events reported from clinical trials are mild and reversible including mainly hypersensitivity reactions, gastrointestinal and sleep disorders. Studies in healthy human volunteers showed no clinically relevant impact on CYP3A, CYP1A2, and CYP2D6. Case reports on interactions could not be verified in clinical trials. Therefore, the benefit/risk balance is considered positive.

Due to the lack of adequate data the use of *Panax ginseng* during pregnancy and lactation is not recommended.

Data on toxicology including data on genotoxicity testing is available for extracts obtained with 40% and 80% ethanol. Herbal preparations obtained with 80% ethanol are not included in the monograph. An Ames-test performed with the 40% ethanolic extract is not completely in accordance with the current OECD-guideline 471. Therefore, at the moment a Community list entry is not proposed.

Annex

List of references