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Committee on Herbal Medicinal Products (HMPC)

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

Draft – Revision 1

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

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.Mey., radix
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% m/m 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 ethanol 60% V/V m) Soft extract (DER 2.5-3.2:1), extraction solvent ethanol 60% V/V

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Pharmaceutical form(s)		Comminuted herbal substance (herbal preparation a)) as herbal tea for oral use. Herbal preparations f, k, l in solid dosage forms for oral use. Herbal preparations g, h, i, j, m in liquid dosage forms for oral use. Herbal preparations b, c, d, e in solid and liquid dosage forms for oral use.
First assessment	Rapporteur	R. Länger
	Peer-reviewer	W. Knöss
Revision	Rapporteur	R. Länger
	Peer-reviewer	H. Foth

Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Panax ginseng* C.A.Mey., radix. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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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. Mey., radix and contains not less than 0.40% for the sum of ginsensosides Rg1 and Rb1 (dried drug).

Constituents (Wichtl 2009, Hänsel & Sticher 2010)

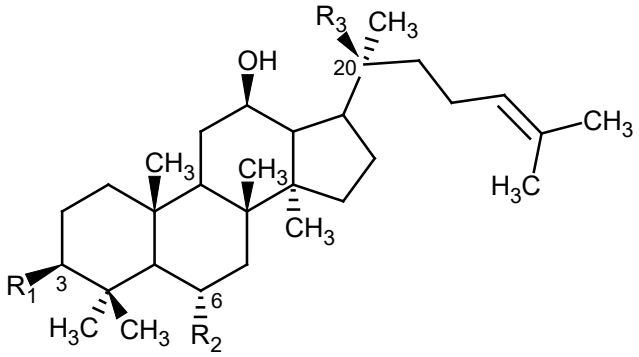
Ginsenosides:

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

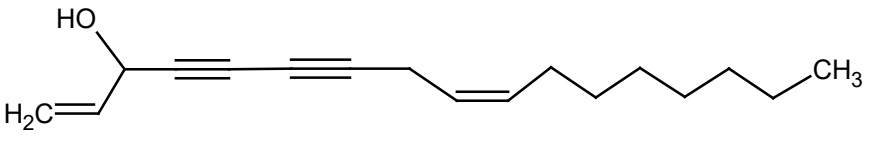
Fig. 1 Structures of main ginsenosides (Glc: β-D-glucopyranosyl, Arabp: α-L-arabinopyranosyl, Araf: α-L-arabinofuranosyl, Rha: α-L-rhamnopyranosyl)

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).



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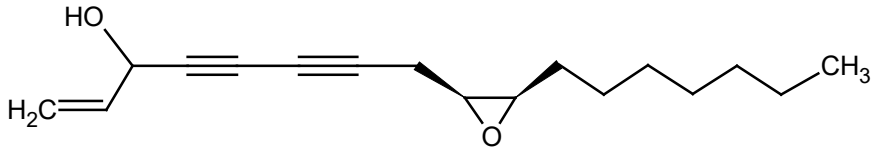

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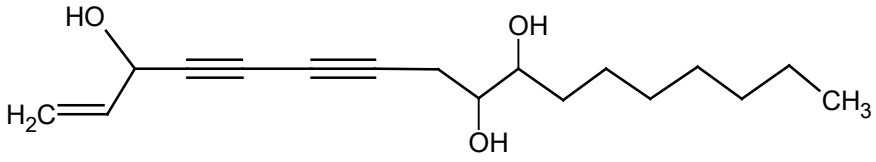


The request for information exchange concerning ginseng radix preparations revealed that several ginseng preparations in combination with other herbal substances/preparations, e.g. ginkgo, or vitamins and minerals are on the market. However, such combinations are not subject of this assessment report.

(3)

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

- 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).

Further herbal preparations see chapter 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.

1.2. Search and assessment methodology

Initial assessment:

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.

Update of literature search, Revision 1:

Pubmed

Search date 30 September 2021, publication date from 1 January 2014 to 30 September 2021

Keywords:

- Panax ginseng: 3797 results
- Panax ginseng and clinical studies: 177 results (reduced to 86 results with applied filter article type 'randomized controlled trial')
- Panax ginseng and drug interactions: 132 results (among them 2 results found by citation matching)
- Panax ginseng and genotoxicity: 10 results

Information from Eudravigilance data base:

77 results concerning "Ginseng" have been identified by 13 July 2021.

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

The focus of assessment during Revision 1 was on controlled clinical trials and safety data. Thus, the above mentioned 86 publications in the field of clinical efficacy/clinical trials as well as 132 publications related to drug interactions were further screened by their abstracts for the probability to induce a change of the monograph. 52 publications thereof were considered to be relevant for further assessment.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
Initial market overview (status 2012)			
Powdered herbal substance (Red Ginseng), standardised to 6% ginsenosides	Asthenia, such as lack of concentration, fatigue, weakness, tiredness, lack of vitality or in convalescence	Hard capsules Adults: 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	WEU, 1996, AT (AT preparation 1)
Dry extract from Ginseng Radix, DER 5:1 (3-7:1), standardised to 4% ginsenosides (sum of Rb_1,	Exhaustion, fatigue lack of concentration, lack of vitality and	Soft capsule	WEU, 1981, AT (AT preparation 2)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Rb_2, Rc, Rd, Re, Rf, Rg_1, Rg_2), extraction solvent 40% EtOH V/V	during convalescence. To strengthen the immune system	Adults: once daily 2 capsules (100 mg dry extract per capsule) Duration of use of 8-12 weeks is recommended. Before re-administering ginseng-preparations a break of 1 month is recommended. Oral liquid Adults: once daily 15 ml of the oral liquid (15 ml contain 140 mg dry extract) Duration of use of 8-12 weeks is recommended. Before re-administering ginseng-preparations a break of 1 month is recommended.	
Radix extract G115	Symptomatic treatment of fatigue, after underlying illness has been excluded	Soft capsules Adults: 2 x 100 mg extract Adolescents from 12 years on: 1x 100 mg	WEU, 2000, BE (BE preparation 1)
Radix, powdered, minimal 8% and max. 10% of total ginsenosides expressed as ginsenoside Rg1	Symptomatic treatment of fatigue, after underlying illness has been excluded	Hard capsules Adults & Adolescents from 12 years on:	WEU, 1997 up to 2010, BE

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
		3 -4 x 300 mg a day	(BE preparation 2)
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	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	Soft capsules Adults: 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) A maximum duration of 3 months is followed by a pause in treatment of 1 month before the preparations are re-administered.	WEU, 2000, DK (DK preparation 1)
Powdered herbal substance	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	Hard gelatine capsules Adults: 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) A maximum duration of 3 months is followed by a pause in treatment of	WEU, 1994, DK (DK preparation 2)

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
		1 month before the preparations are re-administered.	
Powdered herbal substance	Traditionally used in functional asthenia	Hard capsule 2 hard capsules 2 times daily, up to 5 hard capsules, if necessary (390 mg of powder/capsule) 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.	WEU, 1981, FR (FR preparation 1)
Dry extract, DER 3-7:1, extraction solvent EtOH 96% V/V	Traditionally used in functional asthenia	Soft capsule 2-4 soft capsules per day (100 mg dry extract per capsule) 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.	WEU, 1988, FR (FR preparation 2)
Dry extract, DER 3-7:1, extraction solvent EtOH 96% V/V	Traditionally used in functional asthenia	Oral solution	WEU, 1997, FR (FR preparation 3)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		15 ml of oral solution per day (934 mg of extract/100 ml) 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.	
Powdered herbal substance	Traditionally used in functional asthenia	Hard capsule 1 hard capsule 3 times daily (250 mg powdered herbal substance/capsule) 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.	WEU, 1976, FR (FR preparation 4)
Powdered herbal substance	Traditionally used in functional asthenia	Hard capsule 2 hard capsules 2 times daily (500 mg powdered herbal substance/capsule)	WEU, 1976, FR (FR preparation 5)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		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.	
Ginseng radix, powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Hard capsule 3 times daily 1 capsule containing 350 mg Ginseng radix powder	WEU, at least since 1976, DE (DE preparation 1)
Dry extract from Ginseng radix, DER 3-4.5:1, extraction solvent ethanol 30% (m/m)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Pastille 3 times daily 1 containing 100 mg dry extract (in case of particular stress up to 4 times 1	WEU, at least since 1976, DE (DE preparation 2)
Dry extract from Ginseng radix, DER 3-4.5:1, extraction solvent ethanol 30% (m/m)	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.	Coated tablet 2 times daily 2 containing 125 mg dry extract	WEU, at least since 1976, DE (DE preparation 3)
Dry extract from Ginseng radix, DER 3-4.5:1, extraction solvent ethanol 30% (m/m)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Pastille 3 times daily 1 containing 100 mg dry extract (in case of particular stress up to 4 times 1	WEU, at least since 1976 (DE preparation 4)

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
Ginseng radix, powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Hard capsule 3 times daily 1 capsule containing 350 mg Ginseng radix powder	WEU, At least since 1976, DE (DE preparation 5)
Ginseng radix, powder	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity	Hard capsule 2 times daily 2 containing 350 mg Ginseng radix each	WEU, at least since 1976, DE (DE preparation 6)
Soft extract from Ginseng radix, DER 2-6:1, extraction solvent methanol 30% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Oral liquid 2 times daily 15 ml oral liquid (100 ml contains 1.4651g extract)	WEU, at least since 1976, DE (DE preparation 7)
Ginseng radix, powder	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.	Hard capsule 3 times daily 1 capsule containing 350 mg Ginseng radix powder	WEU, at least since 1976, DE (DE preparation 8)
Liquid extract from Ginseng radix, DER 1:1, extraction solvent ethanol 34% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Oral liquid 2 times daily 20 ml oral liquid (20 ml contain 1 ml extract)	WEU, at least since 1976, DE (DE preparation 9)
Ginseng radix, powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Oral liquid	WEU, at least since 1976, DE (DE preparation 10)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		1 time daily 15 ml oral liquid (corresponding to 1.2 g Ginseng radix)	
Dry extract from Ginseng radix, DER 3.5-4.5:1, extraction solvent ethanol 34% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Herbal instant tea 1 time daily 3 g granules dissolved in a cup of hot water (100g granules contain 12 g extract)	WEU, at least since 1976, DE (DE preparation 11)
Ginseng radix, powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Powder 2 times daily 1 g Ginseng radix powder	WEU, at least since 1976, DE (DE preparation 12)
Ginseng radix, powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Hard capsule 2 times daily 1 containing 500 mg Ginseng radix powder	WEU, at least since 1976, DE (DE preparation 13)
Dry extract from Red Ginseng radix, DER 3.5-4.5:1), extraction solvent ethanol 60% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Powder for oral solution 1 time daily 1 sachet of powder containing 0.475 g dry extract	WEU, at least since 1976, DE (DE preparation 14)
Ginseng radix, powder	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.	Powder 3 times daily 500 mg Ginseng radix powder	WEU, at least since 1976, DE (DE preparation 15)

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
Dry extract from Ginseng radix, DER 6-7:1, extraction solvent ethanol 30% (m/m)	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.	Soft capsule 3 times daily 1 containing 90 mg dry extract	WEU, at least since 1976, DE (DE preparation 16) Update Revision 1: MA expired in 06/2019
Dry extract from Ginseng radix, DER 3.2-4:1, extraction solvent ethanol 60% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Oral liquid 2 times daily 30 ml liquid containing 205.8 mg dry extract	WEU, at least since 1976, DE (DE preparation 17)
Red Ginseng radix, powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Hard capsule 3 times daily 2 containing 300 mg Ginseng radix powder each	WEU, at least since 1976, DE (DE preparation 18)
Liquid extract from Ginseng radix, DER 1:0.8-1.2, extraction solvent ethanol 25% (m/m)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Oral liquid 1 time daily 3.3 ml liquid (100 ml=116 g contain 38.28 g liquid extract)	WEU, at least since 1976, DE (DE preparation 19) Update Revision 1: MA expired in 06/2019
Dry extract from Red Ginseng radix, DER 2.2-3.8:1, extraction solvent ethanol 60% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	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)	WEU, at least since 1976, DE (DE preparation 20)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Dry extract from Red Ginseng radix, DER 3-4:1, extraction solvent ethanol 60% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Hard capsule 1 time daily 1 containing 500 mg dry extract	WEU, at least since 1976, DE (DE preparation 21)
Red Ginseng radix, powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Tablet 3 times daily 2 containing 300 mg dry extract each	WEU, at least since 1976, DE (DE preparation 22)
Dry extract from Red Ginseng radix, DER 3-4:1, extraction solvent ethanol 60% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Hard capsule 1 time daily 1 containing 500 mg dry extract	WEU, at least since 1976, DE (DE preparation 23)
Ginseng radix, powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Hard capsule 2 times daily 2 containing 250 mg Ginseng radix powder each	WEU, at least since 1976, DE (DE preparation 24)
Dry extract from Ginseng radix, DER 3-7:1, extraction solvent ethanol 60% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Oral liquid 2-4 times daily 15 ml liquid (100 ml contain 653.34 mg dry extract)	WEU, at least since 1976, DE (DE preparation 25)
Dry extract from Ginseng radix, DER 3-7:1, extraction solvent ethanol 40% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Soft capsule 2 times daily 1 containing 100 mg dry extract	WEU, at least since 1976, DE (DE preparation 26)

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

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
	physical capacity as well as in concentration.	2 times daily 2 containing 350 mg dry extract each	
Dry extract from Ginseng radix, DER 3-4:1, extraction solvent ethanol 60% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Hard capsule 2-3 times daily 1 containing 175 mg dry extract	WEU, at least since 1976, DE (DE preparation 33)
Liquid extract from Ginseng radix, DER 1:1, extraction solvent ethanol 34% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Oral liquid 2 times daily 20 ml liquid (20 ml contain 1 ml liquid extract)	WEU, at least since 1976, DE (DE preparation 34)
Ginseng radix, powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Hard capsule Up to 3 times daily 2 containing 180 mg Ginseng radix powder each	WEU, at least since 1976, DE (DE preparation 35)
Dry extract from Ginseng radix, DER 3-7:1, extraction solvent ethanol 40% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Oral liquid 1 time daily (in the morning) 15 ml liquid containing 200 mg dry extract (up to 30 ml per day is possible)	WEU, at least since 1976, DE (DE preparation 36)
Liquid extract from Ginseng radix, DER 1:1, extraction solvent ethanol 34% m/m	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.	Oral liquid 1-2 times daily 5 ml liquid (100 g=100.75 ml liquid contain 25 g liquid extract)	WEU, at least since 1976, DE (DE preparation 37)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Liquid extract from Ginseng radix, DER 1:1, extraction solvent ethanol 34% V/V	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.	Oral liquid 1-2 times daily 5 ml liquid (100 g=100 ml liquid contain 25 g liquid extract)	WEU, at least since 1976, DE (DE preparation 38)
Extract from Ginseng radix, DER 1:11-13.6, extraction solvent liquor wine	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Oral liquid 1 time daily 20 ml liquid (100 g=96 ml liquid contain 95.2 g extract)	WEU, at least since 1976, DE (DE preparation 39)
Dry extract from Ginseng radix, DER 3-7:1, extraction solvent ethanol 60% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Oral liquid 2-4 times daily 15 ml liquid (100 ml contain 653.34 mg dry extract)	WEU, at least since 1976, DE (DE preparation 40)
Dry extract from Ginseng radix, DER 3-7:1, extraction solvent ethanol 60% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Oral liquid 2-4 times daily 15 ml liquid (100 ml contain 653.34 mg dry extract)	WEU, at least since 1976, DE (DE preparation 41)
Dry extract from Ginseng radix, DER 3.6-5.5:1, extraction solvent ethanol 50% (m/m)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Soft capsule 3 times daily 1 containing 100 mg dry extract	WEU, at least since 1976, DE (DE preparation 42)
Dry extract from Ginseng radix, DER 3-4.5:1, extraction solvent ethanol 30% (m/m)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in	Oral liquid 2 times daily 15 ml liquid (100 ml liquid contain 1.5 g dry extract)	WEU, at least since 1976, DE (DE preparation 43)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
	concentration as well as during convalescence.		
Dry extract from Ginseng radix, DER 3-5:1, extraction solvent ethanol 36% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Soft capsule 2 times daily 2 containing 100 mg dry extract each	WEU, at least since 1976, DE (DE preparation 44)
Dry extract from Ginseng radix, DER 3.6-5.5:1, extraction solvent ethanol 50% (m/m)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Soft capsule 2 times daily 1 containing 220 mg dry extract	WEU, at least since 1976, DE (DE preparation 45)
Liquid extract from Ginseng radix, DER 1:1, extraction solvent ethanol 34% V/V	For the strengthening in case of tiredness and weakness and decreased mental and physical capacity.	Oral liquid 1-2 times daily 15 ml liquid (100 g liquid contain 6.6 g liquid extract)	WEU, at least since 1976, DE (DE preparation 46)
Dry extract from Ginseng radix, DER 3-5:1, extraction solvent ethanol 36% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Soft capsule 2 times daily 2 containing 100 mg dry extract each	WEU, at least since 1976, DE (DE preparation 47)
Ginseng radix, powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Hard capsule 2 times daily 2 containing 250 mg Ginseng radix powder each	WEU, at least since 1976, DE (DE preparation 48)

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
Dry extract from Ginseng radix, DER 3-4:1, extraction solvent ethanol 60% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Oral liquid 3 times daily 20 ml liquid (100 ml liquid contain 0.665 g dry extract)	WEU, at least since 1976, DE (DE preparation 49)
Dry extract from Ginseng radix, DER 3-4.5:1, extraction solvent ethanol 30% (m/m)	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Coated tablet 2 times daily 1-2 containing 125 mg dry extract each	WEU, at least since 1976, DE (DE preparation 50)
Ginseng radix, powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Powder 4-8 times daily 250 mg Ginseng radix powder	WEU, at least since 1976, DE (DE preparation 51)
Dry extract from Ginseng radix, DER 3.3-5:1, extraction solvent methanol 60%	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Coated tablet 3 times daily 1 containing 120 mg dry extract	WEU, at least since 1976, DE (DE preparation 52) Update Revision 1: MA expired in 01/2019
Ginseng radix, powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Hard capsule 2 times daily 2 containing 250 mg Ginseng radix powder each	WEU, at least since 1976, DE (DE preparation 53)
Soft extract from Ginseng radix, DER 2.5-3.2:1, extraction solvent ethanol 60% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Syrup	WEU, at least since 1976, DE (DE preparation 54)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		1 time daily 0.88 g syrup pure or dissolved in a cup of hot water (100 g syrup contain 50 g soft extract)	
Liquid extract from Ginseng radix, DER 1:1, extraction solvent ethanol 34% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Oral liquid 2 times daily 5-10 ml liquid (10 ml liquid contain 1 g liquid extract)	WEU, at least since 1976, DE (DE preparation 55)
Dry extract from Ginseng radix, DER 3-4.5:1, extraction solvent ethanol 30% (m/m)	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.	Oral liquid 1-2 times daily 15 ml liquid (100 ml liquid contain 1.5 g dry extract)	WEU, at least since 1976, DE (DE preparation 56)
Red Ginseng radix, powder	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Hard capsule 1 time daily 4 containing 300 mg Ginseng radix powder each	WEU, 1999, DE (DE preparation 57)
Dry extract from Ginseng radix, DER 3.5-4.5:1, extraction solvent ethanol 34% V/V	As a tonic in case of tiredness and weakness and decreased mental and physical capacity as well as in concentration.	Herbal instant tea 1 time daily 1 sachet containing 0.475 g dry extract dissolved in a cup of hot water	WEU, 1999, DE (DE preparation 58)
Extract from Ginseng radix, DER 1:16-18, extraction	As a tonic in case of tiredness and weakness and decreased mental and	Oral liquid	WEU, at least since 1990, DE (DE preparation 59)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
solvent ethanol 15% (m/m)	physical capacity as well as in concentration.	2 times daily 15 ml liquid (100 g=101.5 ml liquid contain 99.348 g extract)	
Red Ginseng radix in slices	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.	Herbal parts 3 times daily 1 slice of root (for chewing and swallowing	TU, at least since 1976, DE (DE preparation 60)
Standardised dry extract, DER 1.3-3:1; 4% w/w Ginsenosides, extraction solvent EtOH 40% (m/m or V/V?)	As an adjunct in management of patients with impaired general health or those who are convalescent	Soft capsule 2 capsules daily (100 mg dry extract per capsule) duration of use of 8-12 weeks and not recommended for children	WEU, 1984, IE (IE preparation 1) Update revision 1: withdrawn in 11/2012
Standardised dry extract, DER 1.3-3:1; 4% w/w Ginsenosides, extraction solvent EtOH 40% (m/m or V/V)	As an adjunct in management of patients with impaired general health or those who are convalescent	Oral solution 15 ml daily (each 15 ml solution contains 140 mg dry extract) duration of use of 8-12 weeks and not recommended for children	WEU, 1994, IE (IE preparation 2) Update revision 1: withdrawn in 11/2012
Ginseng G115 extract, standardised and highly	As tonic and strengthening agent in tiredness and weakness, in	Oral liquid	WEU, 1990, PL (PL preparation 1)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
concentrate, DER native 3-7:1, extraction solvent EtOH 40% V/V	decreased physical efficiency and in convalescence	15 ml (containing 9.3 mg extract) a day	
Ginseng radix	Traditionally in tiredness, weakness, decreased physical efficiency and reduction of concentration	Herbal tea 2 g once daily	TU, 1999, PL (PL preparation 2)
Ginseng tincture (1:5), extraction solvent ethanol 70% V/V	Traditionally as strengthening agent in tiredness and weakness, in reduction of concentration and in convalescence In geriatrics to improve general feeling	Oral liquid 2.5 ml 2 times daily	TU, 2002, PL (PL preparation 3)
Ginseng G115 extract, standardised and highly concentrate, DER 5:1, extraction solvent EtOH 40% V/V	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 defenses against disease.	Soft capsule 2 capsules at breakfast or one for breakfast and another for lunch. In situations of severe stress the daily dose may be increased up to 4 capsules during the initial treatment period.	WEU, 1995, PT (PT preparation 1)
Ginseng G115 extract, standardised and highly concentrate, DER 5:1, extraction solvent EtOH 40% V/V	No information but probably same indication as for preparation 1	Oral solution 1 measuring cup (15 ml, one tablespoon full) a day, preferably for breakfast.	WEU, 1995, PT (PT preparation 2)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		In situations of severe stress the daily dose may be increased up to 30 ml during the initial period of treatment.	
Dry extract, DER 5:1, 5-7% ginsenosides calculated as ginsenoside Rg1, extraction solvent 70% V/V	Symptomatic treatment of asthenia such as fatigue, weakness	Tablets 2 tablets per day (100 mg of standardised dry extract per tablet) Duration of use no longer than 8 weeks	WEU, 2001, ES (ES preparation 1)
Dry extract, DER 4-6:1, 5-7% ginsenosides, extraction solvent EtOH 50% V/V	Symptomatic treatment of asthenia such as fatigue, weakness	Soft capsules 1 or 2 soft capsules per day (100 mg of standardised dry extract per capsule) Duration of use no longer than 8 weeks	WEU, 2007, ES (ES preparation 2)
Powdered herbal substance	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness	Hard capsules 3-5 capsules per day (300 mg powdered herbal substance per capsule) Duration of use no longer than 8 weeks	TU, 1987, ES (ES preparation 3)

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
Powdered herbal substance	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness	Tablets 3-5 tablets per day (300 mg powdered herbal substance per tablet) Duration of use no longer than 8 weeks	TU, 1996, ES (ES preparation 3)
Panax ginseng C.A. Mey., radix, standardised dry extract (G115), DER 5:1 (3-7:1) Extraction solvent: ethanol 40%	Traditional herbal medicinal product used as a tonic in case of decreased performance such as fatigue and sensation of weakness.	Capsules, soft 1-2 capsules (100 mg of extract per capsule) daily at breakfast/lunch	WEU, 1978, SE Reclassified: TU, 2012, SE (SE preparation 1)
Panax ginseng C.A. Mey., radix, standardised dry extract (G115), DER 5:1 (3-7:1) Extraction solvent: ethanol 40%	Traditional herbal medicinal product used as a tonic in case of decreased performance such as fatigue and sensation of weakness.	Oral solution 10 ml (1 ml 9,3 mg extract) 1-2 times daily at breakfast/lunch	WEU, 1978, SE Reclassified: TU, 2012, SE (SE preparation 2)
Panax ginseng C.A. Mey., radix, standardised dry extract (G115), DER 5:1 (3-7:1) Extraction solvent: ethanol 40%	Traditional herbal medicinal product used as a tonic in case of decreased performance such as fatigue and sensation of weakness.	Capsules soft 1 capsule (40 mg of extract per capsule) daily at breakfast	WEU, 1978, SE Reclassified: TU, 2012, SE (SE preparation 3)
Panax ginseng C.A. Mey., radix, standardised dry extract	Traditional herbal medicinal product used as a tonic in case of decreased	Film-coated tablets	WEU, 2001, SE Reclassified: TU, 2012, SE

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
(G115), DER 5:1 (3-7:1) Extraction solvent: ethanol 40%	performance such as fatigue and sensation of weakness.	1 tablet (100 mg of extract per tablet) daily at breakfast	(SE preparation 4)
Panax ginseng C.A. Mey., radix, standardised dry extract (G115), DER 5:1 (3-7:1) Extraction solvent: ethanol 40%			WEU, 2006, SE Reclassified: TU, 2012, SE (SE preparation 5)
Update of information during Review 1 (2021)			
White Ginseng radix, powder	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Solid dosage forms for oral use *Adults and adolescents over 12 years of age:* SD: 250-1000 mg DD: 1000-2000 mg Up to 3 month, then a pause of 1 month is recommended.	1976, DE, WEU (included in herbal preparation B)
White Ginseng soft extract (2-6:1); extraction solvent: methanol 30% (V/V)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Oral liquid *Adults and adolescents over 12 years of age:* SD: 218 mg DD: 436 mg	1976, DE, WEU (included in herbal preparation H)

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
		Up to 3 month, then a pause of 1 month is recommended.	
White Ginseng dry extract (3-4.5:1); extraction solvent: ethanol 30% (m/m)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Solid and liquid dosage forms for oral use *Adults and adolescents over 12 years of age:* SD: 100-250 mg DD: 250-500 mg Up to 3 month, then a pause of 1 month is recommended.	1976, DE, WEU (included in herbal preparation C)
White Ginseng liquid extract (1:1); extraction solvent: ethanol 34% (m/m)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Liquid dosage forms for oral use *Adults and adolescents over 12 years of age:* SD: 500-1250 mg DD: 1000-2500 mg Up to 3 month, then a pause of 1 month is recommended.	1976, DE, WEU (included in herbal preparation I)
White Ginseng dry extract (3-7:1); extraction solvent: ethanol 40% (V/V)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Solid and liquid dosage forms for oral use *Adults and adolescents over 12 years of age:* SD: 100-200 mg DD: 200-400 mg	1976, DE, WEU (included in herbal preparation C)

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
		Up to 3 month, then a pause of 1 month is recommended.	
White Ginseng dry extract (2.1-3.9:1); extraction solvent: ethanol 40% (V/V)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Oral liquid *Adults and adolescents over 12 years of age:* SD: 166.7-333,4 mg DD: 333,4-666.8 mg Up to 3 month, then a pause of 1 month is recommended.	1976, DE, WEU (included in herbal preparation C)
White Ginseng dry extract (3.6-5.5:1); extraction solvent: ethanol 50% (m/m)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Solid dosage form for oral use *Adults and adolescents over 12 years of age:* SD: 220 mg DD: 440 mg Up to 3 month, then a pause of 1 month is recommended.	1976-12/2022, DE, WEU (included in herbal preparation E)
White Ginseng dry extract (3.5-4.5:1); extraction solvent: ethanol 60% (V/V)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Granules for oral use *Adults and adolescents over 12 years of age:* SD: 360 mg DD 360 mg Up to 3 month, then a pause of 1 month is recommended.	1976, DE, WEU (included in herbal preparation E)

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
White Ginseng dry extract (3-7:1); extraction solvent: ethanol 60% (V/V)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Oral liquid *Adults and adolescents over 12 years of age:* SD: 98 mg DD: 196-392 mg Up to 3 month, then a pause of 1 month is recommended.	1976, DE, WEU (included in herbal preparation E)
White Ginseng soft extract (2.5-3.2:1); extraction solvent: ethanol 60% (V/V)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Syrup *Adults and adolescents over 12 years of age:* SD: 440 mg DD: 440 mg Up to 3 month, then a pause of 1 month is recommended.	1976, DE, WEU (included in herbal preparation G)
White Ginseng soft extract (1.7-2.9:1); extraction solvent: ethanol 70% (V/V)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Soft extract *Adults and adolescents over 12 years of age:* SD: 300-350 mg DD: 600-700 mg Up to 3 month, then a pause of 1 month is recommended.	1976, DE, WEU (included in herbal preparation G)
White Ginseng extract (1:11.0-13.6); extraction solvent: liquor wine	As a tonic in case of tiredness and weakness, in case of decreased	Oral liquid *Adults and adolescents over 12 years of age:*	1976-12/2022, DE, WEU (included in herbal preparation J)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
	mental and physical capacity and decreased concentration.	SD 9.90 g DD 19.80 g Up to 3 month, then a pause of 1 month is recommended.	
Red Ginseng radix, powder	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Solid dosage forms for oral use *Adults and adolescents over 12 years of age:* SD: 600-1200 mg DD: 1200 mg Up to 3 month, then a pause of 1 month is recommended.	1976, DE, WEU (included in herbal preparation K)
Red Ginseng dry extract (3.5-4.5:1): extraction solvent: ethanol 60% (V/V)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Solid and liquid dosage forms for oral use *Adults and adolescents over 12 years of age:* SD: 475 mg DD: 475 mg Up to 3 month, then a pause of 1 month is recommended.	1976, DE, WEU (included in herbal preparation L)
Red Ginseng dry extract (2.2-3.8:1); extraction solvent: ethanol 60% (V/V)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Instant herbal tea for oral use *Adults and adolescents over 12 years of age:* SD: 180 mg DD: 360 mg	1976, DE, WEU (included in herbal preparation L)

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
		Up to 3 month, then a pause of 1 month is recommended.	
Red Ginseng dry extract (3-4:1); extraction solvent: ethanol 60% (V/V)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Solid dosage forms for oral use *Adults and adolescents over 12 years of age:* SD: 500 mg DD: 500 mg Up to 3 month, then a pause of 1 month is recommended.	1976, DE, WEU (included in herbal preparation L)
Red Ginseng soft extract (2.5-3.2:1); extraction solvent: ethanol 60% (V/V)	As a tonic in case of tiredness and weakness, in case of decreased mental and physical capacity and decreased concentration.	Syrup *Adults and adolescents over 12 years of age:* SD: 440 mg DD: 440 mg Up to 3 month, then a pause of 1 month is recommended.	1976, DE, WEU (included in herbal preparation M)
White Ginseng radix, powder	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Solid dosage forms for oral use *Adults:* SD: 360-500 mg DD: 1080-1500 mg Up to 3 month, before re-use a pause from 1 month is recommended. If symptoms worsen	04/2014, DE, TUR (included in herbal preparation B)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		or do not improve after 2 weeks, a doctor should be consulted.	
White Ginseng dry extract (3-4.5:1); extraction solvent: ethanol 30% (m/m)	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Solid dosage forms for oral use *Adults:* SD: 125-250 mg DD: 250-500 mg Up to 3 month.	11/2017, DE, TUR (included in herbal preparation C)
White Ginseng extract (1:1); extraction solvent: ethanol 34% (V/V)	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Oral liquid *Adults:* SD: 1250 mg DD: 1250-2500 mg Up to 3 month.	04/2019, DE, TUR
Red Ginseng radix in slices	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Slices for chewing and swallowing *Adults:* SD: 500 mg DD: 1500 mg Up to 3 month, then a pause from 1 month is recommended.	1976, DE, TU 02/2012, DE, TUR (Preparation has already been excluded in 2012, not possible to define a proper posology.)
Red Ginseng radix, powder	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Solid dosage forms for oral use *Adults and elderly:* SD: 600-1200 mg DD: 1200-1800 mg	04/2013, DE, TUR (included in herbal preparation K)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		Up to 3 month, before re-use a pause from 1 month is recommended. If symptoms worsen or do not improve after 2 weeks, a doctor should be consulted.	
Red Ginseng dry extract (2-4.5:1); extraction solvent: ethanol 60% (V/V)	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Solid dosage forms for oral use *Adults:* SD 500 mg DD 500 mg Up to 3 month. If symptoms worsen or do not improve after 2 weeks, a doctor should be consulted. Before re-use a pause from 1 month is recommended.	12/2017, DE, TUR (included in herbal preparation L)
Red Ginseng soft extract (2.5-3.2:1); extraction solvent: ethanol 60% (V/V)	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Syrup 15 g soft extract/30 g syrup *Adults:* SD = DD: 1.23 g Red Ginseng radix Up to 3 month, before re-use a pause from 1 month is recommended.	2013, DE, TUR (included in herbal preparation M)

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
Ginseng radix, herbal substance, comminuted	Traditionally used in a form of infusion to counteract fatigue and weakness, decreased physical performance and decreased concentration. Traditionally in convalescence.	Herbal tea, infusion. 2g (measuring spoon) pour with a glass of boiling water (200-250ml). The infusion drink in divided doses during a day. Not use for longer than 1 month without consultation.	NA, 2000, PL (included in herbal preparation A)
300 mg of *Panax ginseng* C.A. Mey., radix	THMP for fatigue, physical or psychological exhaustion and weakness	Adults only 3 - 5 capsules per day	REDSENG 300 mg capsules April, 2012 (included in herbal preparation B)
300 mg of *Panax ginseng* C.A. Mey., radix	THMP for fatigue, physical or psychological exhaustion and weakness	Adults only 3 - 5 tablets per day	REDSENG 300 mg tablets April, 2012 (included in herbal preparation B)

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

Not applicable.

Information on other products marketed in the EU/EEA (where relevant)

Additional information BE:

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 notavailable. 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.

Additional information DK:

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 FR:

There exists only one combination product (with *Menyanthes trifoliata* L. and ascorbic acid).

Additional information DE:

No German Standard Marketing Authorisations, neither for the single active ingredient nor for combination products.

Additional information IE:

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

Additional information IT:

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.

Additional information LV:

Only a combination with Ginkgo is on the market.

Assessor's comment:

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.

2.1.2. Information on products on the market outside the EU/EEA

Not applicable.

2.2. Information on documented medicinal use and historical data from literature

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), see table 2.

Each of the preparations listed in table 1 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 table 1).

Table 2: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form** **Posology** **Duration of use**	**Reference**
Comminuted herbal substance	Neurasthenia, Neuralgia, Insomnia, Hypotonia	Decoction for oral use Single dose: 1-2 g of herbal drug Daily dose: 2-6 g Dosage frequency: 3 times daily	British Herbal Pharmacopoeia (1983) List & Hörhammer (1977) Blaschek *et al.* (2008)

2.3. Overall conclusions on medicinal use

Most of the herbal preparations authorised in the EU member states as listed in table 1 fulfil the criteria of at least 30 years of medicinal use as defined in Dir. 2001/83/EC. None of the preparations fulfils the criteria for Well established medicinal use as defined in Dir. 2001/83/EC. The proposed indication is based on the wording of the indications as authorised in respective member states. However, 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.

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. A duration of use up to 3 months is possible. 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.

For all herbal preparations the route of administration is oral use.

Although, at least until 2012, ginseng preparations on the German market have been authorised for oral use in adults and adolescents over 12 years, the proposed age limit for the monograph is adults and elderly.

Revision 1:

In course of revision 1 an updated Market Overview (Market OV 2021) revealed a herbal preparation not yet included in the monograph (new proposed TU herbal preparation m, on the market since 1976). Furthermore, four herbal preparations require an update (preparations e, i, j and k; modification in posology or extraction solvent). More precise information has been presented on the starting material of several herbal preparations present on the German market (white or red ginseng), for details see table 1.

In brief, the following changes are proposed for the monograph, justified by the respective rationale:

Herbal preparation e:

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

Posology:

Present: Single dose: 98-220 mg, daily dose: 196-525 mg; dosage frequency: 2-4 times daily

Proposed: Single dose: 98-360 mg, Daily dose: 196-525 mg; dosage frequency: 1-4 times daily

Rationale: Market OV 2021 [DE, WEU preparation 8.; White ginseng, dry extract (3.5-4.5:1); extraction solvent: ethanol 60% (V/V); posology: single dose 360 mg, daily dose 360 mg, on the market since 1976]

Herbal preparation i:

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

Posology: Single dose: 500 mg - 1250 mg, daily dose: 900 mg – 2500 mg; dosage frequency: 1-2 times daily

Proposed extraction solvent: ethanol 25% m/m – 34% m/m

Rationale: Market OV 2021 [DE, WEU preparation 4.; White ginseng, liquid extract (1:1); extraction solvent: ethanol 34% (m/m); posology: single dose: 500-1250 mg, daily dose: 1000-2500 mg), on the market since 1976]

Herbal preparation j:

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

Posology:

Present: Single dose: 19.4 ml, daily dose: 19.4 ml; dosage frequency: once daily

Proposed: Single dose: 9.90 g, daily dose: 19.80 g; dosage frequency: 2 times daily

Rationale: Market OV 2021 [DE, WEU preparation 12.; White ginseng, liquid extract (1:11.0-13.6); extraction solvent: liquor wine; posology: single dose 9.90 g, daily dose 19.80 g;]

This preparation has originally been reported in 2012 with the posology listed above (present) as being on the market since 1976. In 2004 the renewal of the market authorization was granted with the posology as proposed now. The proposed change is based on regulatory practice and therefore considered justified. Moreover, as the single dose is reduced, safety concerns are not expected.

Herbal preparation k:

Powdered herbal substance

Posology:

Present: Single dose: 600 mg, daily dose: 1800 mg; dosage frequency: 3 times daily

Proposed: Single dose: 600-1200 mg, daily dose: 1200-1800 mg; dosage frequency: 1-3 times daily

Rationale: Market OV 2021 [DE, TU preparation 5.; Red ginseng radix, powder; posology: single dose: 600-1200 mg, daily dose: 1200-1800 mg, on the market since 04/2013]. The daily dose is already covered by the current preparation K). As the registration was granted under current legislation, also the higher single dose is considered to be safe and justified.

Herbal preparation m (new):

Soft extract (DER 2.5-3.2:1), extraction solvent ethanol 60% V/V

Posology: Single dose 440 mg, Daily dose: 440 mg; Dosage frequency: once daily

Rationale: Market OV 2021

- DE, WEU preparation 17.; Red ginseng, soft extract (2.5-3.2:1); extraction solvent: ethanol 60% (V/V); posology: single dose: 440 mg, daily dose: 440 mg; on the market since 1976;
- DE TU preparation 7; Red Ginseng, soft extract (2.5-3.2:1); extraction solvent: ethanol 60% (V/V); posology: Syrup, 15 g soft extract/30 g syrup, single dose = daily dose: 1.23 g Red Ginseng radix; on the market since 2013

For complete overview of herbal preparations as proposed for the EU herbal monograph see table 3

Table 3: Overview of evidence on period of medicinal use

Herbal preparation **Pharmaceutical form**	**Indication**	**Posology, Strength**	**Period of medicinal use**
White ginseng (TU)			
a) Comminuted herbal substance as decoction for oral use	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Single dose: 1000 – 2000 mg Daily dose: 2000 – 6000 mg Dosage frequency: 3 times daily	According to references British Herbal Pharmacopoeia (1983) List & Hörhammer (1977) Blaschek *et al.* (2008)
b) Powdered herbal substance	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Single dose: 250 – 1200 mg Daily dose: 600 – 2000 mg Dosage frequency: once daily (1200 mg), 2 -8 times daily	DE preparations 1, 5, 6, 8, 10, 12, 13, 15, 24, 27, 29, 32, 35, 48, 51, 53 FR preparations 1, 4, 5
c) Dry extract (DER 2-7:1), extraction solvent ethanol 34-40% V/V	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Single dose: 90 – 360 mg Daily dose: 200 – 670 mg Dosage frequency: 1 – 4 times daily	DE 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)	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	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	AT preparation 2 BE preparation 1 DK preparation 1 IE preparations 1, 2 PL preparation 1 PT preparations 1,2

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
			SE preparations 1, 2, 3, 4, 5
e) Dry extract (DER 3-7:1), extraction solvent ethanol 57.9% V/V (= 50% m/m) – 60% V/V	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Single dose: 98 –360 mg Daily dose: 196 – 525 mg Dosage frequency: 1 – 4 times daily	DE preparations 17, 25, 33, 40, 41, 42, 45, 49; DE WEU preparation 8 (Market OV 2021)
f) Dry extract (DER 3.3-5:1), extraction solvent methanol 60% V/V	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Single dose: 120 mg Daily dose: 360 mg Dosage frequency: 3 times daily	DE preparation 52
g) Soft extract (DER 1.7-3.2:1), extraction solvent ethanol 60%-70% V/V	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Single dose: 300 - 440 mg Daily dose: 440 – 700 mg Dosage frequency: once (440 mg) or 2 times daily	DE preparations 31, 54
h) Soft extract (DER 2-6:1), extraction solvent methanol 30% V/V	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Single dose: 219.8 mg Daily dose: 439.6 mg Dosage frequency: 2 times daily	DE preparation 7
i) Liquid extract (DER 1:0.8-1.2), ethanol 30.5% V/V (= 25% m/m) – 34% m/m	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Single dose: 500 mg – 1250 mg Daily dose: 990 mg – 2500 mg	DE preparations 9, 19, 34, 37, 38, 46, 55; DE WEU preparation 4 (Market OV 2021)

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
		Dosage frequency: 1-2 times daily	
j) Liquid extract (DER 1:11-13.6), extraction solvent liquor wine	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Single dose: 9.90 g Daily dose: 19.80 g Dosage frequency: 2 times daily	DE preparation 39; DE WEU preparation 12 (Market OV 2021)
Red Ginseng (TU)			
k) Powdered herbal substance:	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Single dose: 600 – 1200 mg Daily dose: 1200 - 1800 mg Dosage frequency: 1 - 3 times daily	DE preparations 18, 22; DE TU preparation 5 (Market OV 2021)
l) Dry extract (DER 2-4.5:1), extraction solvent ethanol 60% V/V	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Single dose: 180 – 500 mg Daily dose: 360 – 500 mg Dosage frequency: once (475 mg or 500 mg) or 2 times daily	DE preparations 14, 20, 21, 23
m) Soft extract (DER 2.5-3.2:1), extraction solvent ethanol 60% V/V	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.	Single dose: 440 mg Daily dose 440 mg Dosage frequency: once daily	DE WEU preparation 17 (Market OV 2021), DE TU preparation 7 (Market OV 2021)

Herbal preparations not included in the monograph:

- 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.

  Update revision 1: herbal preparation 2 is no longer on the French market

- 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.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

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.

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). However, in many cases, especially in older studies, the ginseng preparations are not characterized sufficiently. In the following section pharmacological data on the well-defined herbal preparation G115 [corresponding to herbal preparation 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)] as well as on isolated ginsenosides, polyacetylens, and polysaccharides is presented.

Table 4: Overview of the main non-clinical data/conclusions

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
Preparations of the monograph				
Herbal preparation 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) usually referred as G115	25 mg/kg/p.o.	*In vivo* (mice) Effects of G115 on anti-inflammatory cytokine production and toll-like receptor 4 (TLR4) RNA expression in male 6-week- old BALB/c pathogen-free mice during 4 weeks of swimming stress	Pannacci *et al.* (2006)	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.
Herbal preparation 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) usually referred as G115	2 mg/kg/p.o 200 mg/kg/p.o.	*In vivo* (rats) Effects of G115 on balloon injury-induced neointima formation (restenosis) in Sprague-Dawley rats.	Wu *et al.* (2001)	Neointima-to-lumen area ratio of balloon injured rat carotid arteries was reduced 77.3% by G115 as compared to the sham-operated control.
Herbal preparation 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) usually referred as G115	Tissue bath 0.18, 0.36, 0.72, 1.44, and 2.88 mg/ml	*Ex vivo* (rats, aortic strips) Effects of G 115 on contractions of aortic strips	Wu *et al.* (2001)	Norepinephrine-induced vasocontraction was antagonized in 21% and 44% by 1.44 mg/ml and 2.88 mg/ml of G115, respectively.

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
Herbal preparation 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) usually referred as G115	3 mg/kg/p.o. 10 mg/kg/p.o. 100 mg/kg/p.o.	*In vivo* (rats) Effects of G115 on hepatic antioxidant function after exhaustive exercise.	Voces *et al.* (1999)	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.
Herbal preparation 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) usually referred as G115	Oral Mice: 0.25, 75, 200 or 500 mg/kg/day in drinking water Rats: 100 mg/kg/day in drinking water	*In vivo* (rats, mice) Neuroprotective actions of the ginseng extract G115 in two rodent models of Parkinson's disease.	Van Kampen *et al.* (2003)	Oral administration of G115 appeared to provide protection against neurotoxicity in rodent models of Parkinson's disease.
Herbal preparation 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) usually referred as G115	50, 100, 200, and 400 mg/kg/p.o. 100 mg/kg/i.p.	*In vivo* (mice) Effects of orally applied G115 on morphine analgesia, development of morphine-induced tolerance and physical dependence, hepatic glutathione levels. Effects of intraperitoneally applied G115 on the dopamine receptor supersensitivity and the reverse tolerance to the locomotor	Kim *et al*. (1990)	The authors concluded that G115 could be developed for the treatment of morphine tolerant/dependent patients.

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
		accelerating effect of morphine.		
Herbal preparation 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) usually referred as G115	2.3, 4.7, and 9.3 mg/kg i.p.	*In vivo* (rabbits) Effect of G115 on the metabolic activity and electrocorticogram of the rabbit's brain.	Samira *et al*. (1985)	G115 was found to have a stimulant, desynchronizing action on the electrocorticogram of conscious rabbit brain
Herbal preparation 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) usually referred as G115	Incubation of brain tissue with 23 and 46 µg/ml	*In vitro* (brain tissue)	Samira *et al*. (1985)	Presence of G115 indicated changes in the metabolic pathways and seemed to improve the energy balance of neuronal cells.
Single substances				
Effects of isolated ginsenosides on metabolism				
Rb_1	1 or 10 mg/kg b.w. Rb_1 i.p. once daily for 3 days	*In vivo* (rats) Influence on blood lipid levels in rats	Park *et al.* (2002)	Contents of triglycerides and cholesterol in the liver were decreased, plasma levels of triglycerides and β- lipoprotein were unaffected
Rb_1	5 mg/100 g b.w. Rb_1 i.p.	*In vivo* (rats) Influence on activity of HMG-CoA in rats on a high fat diet	Ikehara *et al.* (1978)	Activity of HMG-CoA is repressed by a high fat diet, administration of Rb_1 reverted this effect

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
Rb_2	single dose of 10 mg Rb_2 in saline solution i.p.	*In vivo* (rats) Influence on blood lipid levels in rats on a high cholesterol diet	Yokozawa *et al.* (1985a)	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
Rb_2	i.p. 10 mg Rb_2 in saline solution daily for 6 days	*In vivo* (rats) Influence on different metabolic parameters in streptozotocin induced diabetic rats	Yokozawa *et al.* (1985b)	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
Rb_2	single dose of 10 mg Rb_2 in saline solution i.p.	*In vivo* (rats) Influence on different metabolic parameters in time course experiments in rats	Yokozawa *et al.* (1984)	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
Re	5, 10 or 20 mg/kg b.w. p.o.	*In vivo* (rats) Influence on blood glucose, cholesterol and triglyceride levels in streptozotocin induced diabetic rats	Cho *et al.* (2006)	Significant reduction in blood glucose, cholesterol and triglyceride levels in diabetic rats treated with Re. Levels of glutathione and malonyldialdehyde in the eye

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
				and kidney were restored to normal values
Rh_2	single (0.1-1.0 mg/kg) and repeated doses (3 times daily 1.0 mg/kg) i.v.	*In vivo* (rats) Influence on blood glucose levels and insulin resistance (induced insulin resistance by fructose-rich diet, streptozotocin-induced diabetic rats)	Lee *et al.* (2007, abstract only)	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
Rh_2	Rats: single dose of 1.0 mg/kg b.w. i.v. 1.0 mg/kg b.w. i.v. three times daily Mice: single dose of 1.0 mg/kg b.w. i.v.	*In vivo* (rats, mice) Influence on blood glucose and insulin levels in diabetic rats and mice	Lai *et al.* (2006)	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
Rh_2	single dose administration of 0.1, 0.5, or 1.0 mg/kg b.w. i.v.	*In vivo* (rats)	Lee WK *et al.* (2006)	Dose dependent decrease of plasma glucose levels

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
	single dose administration of 1.0 m/kg b.w. i.v. in presence of different concentrations of atropine, 4-diphenylacetoxy-N-methylpiperidine methiodide (4-DAMP), pentolinium, hexamethonium, hemicholinium-3, and vesamicol	Influence on blood glucose and insulin levels in rats		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 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
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: 10 mg/kg b.w. compound K 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.*	*In vivo* (mice) Effects on blood glucose levels in diabetic mice	Yoon *et al.* (2007)	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
Malonyl- ginsenosides	Different groups, i.v. for four consecutive days of: 30, 60, 120 mg/kg of malonyl-ginsenosides	*In vivo* (mice) Effects on blood glucose levels in	Liu Z *et al.* (2009)	At a dose of 120 mg/kg b.w i.v. of malonyl- ginsenosides reduced the fasting blood

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
	120 mg/kg total saponins 120 mg/kg panaxadiol 4.5 mg/kg malonic acid 120 mg/kg panaxadiol mixed with malonic acid	streptozotocin-induced diabetic rats		glucose level of diabetic mice and improved glucose tolerance. Panaxadiol, malonic acid and a mixture of both compounds showed no effect
Effects of isolated ginsenosides on the cardiovascular system				
Rb_1	40 mg/kg i.v	*In vivo* (rats) Myocardial ischemia and reperfusion model (30 min of coronary occlusion followed by 120 min reperfusion)	Wu *et al.* (2011)	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)
Rb_1	4 different groups (control, hyperhomocysteine, Rb_1 treatment, hyperhomocysteine+Rb_1) ***Assessor's comment:*** *posology not given in the abstract*	*In vivo* (rats) *In vitro* (HUVEC) Influence on homocysteine-induced endothelial dysfunction and ghrelin expression, aortic ring assay, enzyme-linked immunosorbent assay	Xu *et al.* (2011, abstract only)	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 upregulated the NO signaling pathway

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
Rb_1	0.35 mM via an osmotic pump for 4 weeks	*In vivo* (mice) Effects of Rb_1 on intimal hyperplasia in a guidewire injury animal model	Chai *et al.* (2009)	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
Rb_1	40 mg/kg i.v.	*In vivo* (rats) Myocardial ischemia and reperfusion injury model	Wang *et al.* (2008)	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)
Rb_1	10 and 40 mg/kg i.p.	*In vivo* (rats) Investigation of preventive and curative effects of Rb_1 on right ventricular	Jiang *et al.* (2007)	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

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
		hypertrophy induced by monocrotaline		
Rb_3	5, 10, 20 mg/kg orally for three days prior to myocardial ischemia-reperfusion	*In vivo* (rats) Ischemia-reperfusion (30 min ischemia followed by 24 h reperfusion) model	Shi *et al.* (2011)	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
Rd	20 mg/kg/day i.p. for 12 weeks (preventive) 20 mg/kg/day i.p. for 5 weeks after 7 weeks of high- fat diet (curative)	*In vivo* (mice) Investigation of the effect of Rd on atherosclerosis in apoE knockout mice	Li J *et al.* (2011)	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
Re	20 mg/kg i.v. of Re 10 min before ischemia	*In vivo* (rats) Ischemia (30 min)/reperfusion (6 h) model to investigate the effects of Re on	Liu *et al.* (2002)	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

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
		myocardial ischemia/reperfusion		increase of the ratio of Bcl-2/Bax
Rg_1	15 mg/kg/day i.p. alone or in combination with orally applied L-arginine or N^G-nitro-L-arginine-methyl ester for 21 consecutive days	*In vivo* (rats) Influence of Rg_1 on left ventricular hypertrophy induced by abdominal aorta coarctation and its mechanism of action	Deng *et al.* (2010)	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
Rg_1	3.75, 7.5, and 15 mg/kg/day i.p. for 21 consecutive days	*In vivo* (rats) Influence of Rg_1 on left ventricular hypertrophy induced by abdominal aorta coarctation and its mechanism of action	Deng *et al.* (2009)	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
Rg_1	Sterilized acellular patch was submerged in an aqueous solution of 10 mg/ml of Rg_1 for 36 h	*In vivo* (rabbits) 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	Chang *et al.*(2006)	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 observed in 3 of the 5 studied animals at 3 months after surgery

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
Ro	10 or 50 mg/kg orally 1 h prior to the injection of endotoxin	*In vivo* (rats) Antithrombic activity in an experimental model of disseminated intravascular coagulation induced by infusion of endotoxin or thrombin	Matsuda *et al.*(1986)	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
20(S)-protopanaxatriol	orally for 7 days ***Assessor's comment:*** *posology not given in the abstract*	*In vivo* (rats) Model of myocardial injury induced by isoproterenol	Han *et al.* (2011, abstract only)	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 of isolated ginsenosides on the nervous system/behaviour				
Rb_1, Rg_1, Rg_3, Ro, compound K, protopanaxadiol	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.	*In vivo* (mice) Investigation of antidepressant activity in ICR albino female mice (ovariectomized) in forced swimming test and investigation of general motor activity.	Yamada *et al.* (2011)	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

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
				mice
Rb_1	20 mg/kg i.v. treatment was acute (single dose), chronic (twice daily for 7 days), preventive (twice daily for 14 days prior to tryptophan or tryptophan-free diet)	*In vivo* (mice) Object recognition memory, forced swimming test and locomotor activity tested 1h after treatment with single dose Brain samples investigated for neurotransmitter concentration (e.g. tryptophan, kynurenine, 5-HT, dopamine, norepinephrine) and enzyme activity (tryptophan hydroxylase, MAO, aromatic amino acid decarboxylase)	Hao *et al.* (2011)	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; pre-treatment with clomiphene blocked the Rb_1 effects
Rb_1	2 mg/kg b.w. in drinking water for 30 days	*In vivo* (rats) Behavioural test (Morris water maze), cell survival/cell prolongation in the hippocampus: BrdU incorporation	Liu *et al.* (2011)	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
Rb_1	20 mg/kg i.v.	*In vivo* (rats) Neurobehavioural testing using the	Li Y *et al.* (2011, abstract only)	Rb_1 reduced significantly the brain edema and improved neurobehavioral functioning, histological examination

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
		spontaneous activity scoring system, brain water content, and histological examination of the basilar artery		revealed a significant reduction in basilar artery vasospasm and lumen thickness
Rb_1	In vivo: 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	*In vivo* (rats) After coagulation of left middle cerebral artery and intracerebroventricular infusion of Rb_1, animals were subject to Morris water-maze test, Inclined screen-test and Rotating rod-test; brains were examined morphologically *In vitro* 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	Zhang *et al.* (1998)	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 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*
Rb_1	10, 100 nmol/L, icv	*In vivo* (rats) The effect of Rb_1 on the population spike (PS) amplitude and	Wang & Zhang (2003)	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

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
		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		maintenance phases of LTP and increased LTP expression in a dose-dependent manner in anaesthetized rats
Rb_1	0.25, 2.5, 5.0 mg/kg b.w. i.p	*In vivo* (cockerels) 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. Separation distress was evaluated (anxiety setting using chambers with or without mirrors for separated animals).	Churchill *et al.* (2002)	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.
Rb_1, Rg_1	2.5, and 5.0 mg/kg i.p.	*In vivo* (rats)	Wang & Lee (2000)	Pre-treating the animals with Rb_1 but not Rg_1 increased thermogenesis as well as cold

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
		Effects on cold tolerance of young and elderly rats were examined by measuring heat production, oxygen consumption and carbon dioxide production		tolerance in young rats and elderly rats
Rb_1	Different treatment groups: 2.5 or 25 ng Rb_1 injected into the left lateral ventricle immediately after TIA Osmotic minipump was implanted subcutaneously releasing 60 or 600 ng/day for 7 days into the lateral ventricle 10 or 20 mg/kg i.p. of Rb_1 once daily for 7 days before or after 3.5 min of forebrain ischemia	*In vivo* (Mongolian gerbils) 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 *In vitro* Antioxidative properties were studied in a cell culture model using hippocampal neurons of 17 day old rat embryos treated with $FeSO_4$	Lim *et al.* (1997)	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*
Rb_1, Malonyl- ginsenoside Rb_1	icv application of 0.5-50 nmol Rb_1 and Rb_1-m	*In vivo* (rats)	Abe *et al.* (1994, abstract only)	Rb_1 did not affect the basal synaptic responses evoked by

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
		Investigation of anaesthetised rats		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
Rb_1	Infusion of 0.05, 0.10, and 0.20 µmol Rb_1 into the third cerebroventricle Injection of 0.01 µmol of Rb_1 into the hypothalamic ventromedial nucleus and into the hypothalamic area	*In vivo* (rats)	Etou *et al.* (1988, abstract only)	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 levels were unaffected. Microinjection into the hypothalamic ventromedial nucleus decreased food intake, injection into the lateral hypothalamic area did not.
Rb_3	30, 75, and 150 mg/kg b.w. were administered intragastrically	*In vivo* (mice, rats) Open field test, forced swim test, tail suspension test, and learned helplessness procedure were applied as a behavioural despair model; Locomotor activity test, novelty-suppressed feeding test, and sucrose preference test served for the assessment of	Cui *et al.* (2012)	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;

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
		the behaviour in chronic mild stress conditions; Levels of monoamine neurotransmitters, frequency and amplitude of action potentials were investigated in different brain regions		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 in rats
Rd	In vivo: Pre-treatment with 10 mg/kg Rd 7 days prior to injection of OA, animals were sacrificed 2 weeks later ***Assessor's comment:*** *The route of administration in the animal model is not described* In vitro: Incubation of cells with 2.5 or 5.0 µmol/L for 12 h	*In vivo* (rats) AD model induced by the microinjection of 200 ng okadaic acid (OA) into cerebral ventricle Brain tissue was investigated histologically and assayed for protein phosphatase 2A activity *In vitro* Neuroprotective effects of Rd on cultured cortical neurons were investigated	Li L *et al.* (2011)	Pre-treatment with Rd reduced OA-induced neurotoxicity and tau hyperphosphorylation by enhancing the activity of protein phosphatase 2A
Rd	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 vivo* (mice) Behavioural tests in mice with middle cerebral artery	Ye *et al.* (2011a)	Rd at doses of 10-50 mg/kg b.w. significantly reduced both cortical and striatal infarct volume; furthermore improvement in neurological

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
		occlusion: postural reflex test, forelimb placing test *In vitro* 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 behavioural tests and focusing on the effects of Rd on mitochondria and the mechanism of action*		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
Rd	1 or 5 mg/kg b.w. of Rd once daily for 30 days ***Assessor's comment:*** *The route of administration is not mentioned in the abstract, the full article was not available*	*In vivo* (mice) Parameters of the antioxidative defence system were measured in senescence-accelerated mice	Yokozawa *et al.* (2004, abstract only)	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
Rb_1, Rb_2, Rc, Rd, Re, Rf, Rg_1, Rg_2, Rg_3	50 µg (except Rd: 1-50 µg) i.c.v. injection	*In vivo* (mice) Survival time of the animals pretreated with single	Lee JK *et al.* (2003)	Administration of Rd i.c.v. attenuated the KA-induced lethal toxicity

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
		ginsenosides was examined after induction of neurotoxicity (intracerebroventricular microinjection of kainic acid)		
Rf	10^{-14}, 10^{-12}, 10^{-10} mg/kg i.p	*In vivo* (mice) Tolerance studies in mice with U50-induced analgesia; flumazenil (0.1 mg/kg) and picrotoxin (1 mg/kg) were co-administered to get insight into the mechanism of action of Rf	Nemmani & Ramarao (2003)	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
Rg_1	30 mg/kg i.p. once daily 2 h after the second morphine injection	*In vivo* (rats) The influence of Rg_1 on morphine induced impairment (10 mg/kg morphine s.c. twice daily) in the Morris water maze test was investigated	Qi *et al.* (2009)	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.
Rg_1	4.0 mM solution of Rg_1 in phosphate buffered saline was infused continuously via an osmotic minipump into the third cerebroventricle	*In vivo* (rats) Effects of Rg_1 on IL-1β induced suppression of food and water intake and body temperature were investigated	Kang *et al.* (1995)	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

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
Rg_1	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 Continuous infusion of 4.0 mM Rg_1 in phosphate buffered saline via an osmotic minipump	*In vivo* (rats) Effects of Rg_1 on modulation of ingestive behaviour were investigated	Fujimoto *et al.* (1989)	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 and decreased ambulation that was produced by elevation of environmental temperature; rats maintained body weight and rectal temperature unchanged
Rg_2	2.5, 5.0, and 10.0 mg/kg i.v.	*In vivo* (rats) Effects of Rg_2 on memory impairment induced in rats in a vascular dementia model (occlusion of the middle cerebral artery for 1 h, circulation was restored for 48 h) were investigated applying the Y-maze test	Zhang G *et al.* (2008)	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
Rg_2	20 mg/kg Rg_2 was administered i.p. repeatedly	*In vivo* (rats) Effects of Rg_2 on acquisition, retention, and retrieval were examined in a two-way active avoidance method	Ma & Yu (1993)	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

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions of the authors
Rb_1, Rg_3, Rh_2	10, 20, 40 mg/kg p.o,	*In vivo* (mice) Influence of ginsenosides on learning and memory in mice (scopolamine induced learning deficit model) was investigated in passive avoidance test, Y-maze test and Morris water maze test	Yang YH *et al.* (2009)	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
Rh_2	100 mg/kg orally	*In vivo* (rats) Effects of Rh_2 in rats with induced transient cerebral ischemia (occlusion of the middle cerebral artery)	Park *et al.* (2004)	Orally administered Rh_2 significantly reduced the infarct area caused by MCA occlusion.
20(S)-protopanaxadiol	3.75, 7.5, and 15 mg/kg were applied orally in tail suspension tests and forced swimming tests 3.3, 6.6, and 13.3 mg/kg were applied orally in the passive avoidance tests and sweet water consumption tests	*In vivo* (mice, rats) Investigation of antidepressant effects of 20(S)-protopanaxadiol in mice and rats, applying tail suspension test , forced swimming test, passive avoidance test, sweet-water consumption test and other tests	Xu *et al.* (2010)	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

***In vitro* studies with isolated ginsenosides:**

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-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.

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).

3.1.2. Secondary pharmacodynamics

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 constituents (ginsenosides, polyacetylens) 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 possible relevance for the observed clinical effects is presented.

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).

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.

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.

Neuroprotective effects (Nie *et al.* 2006, Nie *et al.* 2008)
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. Pre-treatment 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.

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

3.1.3. Safety pharmacology

No information available

3.1.4. Pharmacodynamic interactions

Limited information is available, see summary of studies and assessor's comments in section 5.5.4.

3.1.5. Conclusions

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. Therefore, final conclusions on the efficacy of ginseng cannot be drawn.

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 tumour 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 studies included in 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

Toxicological data are available for two herbal preparations:

- **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**

- **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)]**

This extract has been investigated in the US National Toxicology Program 2011 (NTP TR 567), 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. The results of the NTP-investigations are also briefly reported in the following subsections

3.3.1. Single dose toxicity

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:

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.

3.3.2. Repeat dose toxicity

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:

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.

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)]

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.

2-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 behavioural 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.

3.3.3. Genotoxicity

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:

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.

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)]

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, 3.3.2).

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].

3.3.4. Carcinogenicity

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)]

Under the conditions of the 2-year gavage studies (see above, 3.3.2), 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.

3.3.5. Reproductive and developmental toxicity

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:

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.

3.3.6. Local tolerance

No information on systematic studies on local tolerance available.

3.3.7. Other special studies

Not applicable.

3.3.8. Conclusions

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 European Union List Entry is not proposed.

3.4. Overall conclusions on non-clinical data

In numerous studies (in animal models as well as in vitro) extracts, fractions and isolated compounds of *Panax ginseng* showed a broad set of biological activities. However, concentrations of isolated compounds applied in animal models are often higher than expected in the therapeutic application of ginseng. Therefore, firm conclusions on the pharmacological effects and possible mechanism of action cannot be drawn.

Data from formal toxicity studies are available for two herbal preparations. Adequate tests on reproductive toxicity have not been performed. No signs of genotoxicity were observed in an AMES-test (Salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100) with and without metabolic activation using the extract G115 (herbal preparation d). 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. An Ames-test performed with the 80% ethanolic extract (no corresponding herbal

preparation in the monograph) fully complies with the current OECD guideline 471 and showed a negative outcome. After 2 years of oral administration of an extract prepared with ethanol 80% in dosages of up to 5000 mg/kg b.w. no signs of carcinogenicity were observed in mice or rats. Currently the development of a European Union 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.

Scaglione *et al.* (1990)

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.

Cognition and cerebrovascular function:

Kennedy *et al.* (2003)

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.

Scholey & Kennedy (2002)

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".

Quiroga & Imbriano (1979)

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):

Tawab *et al.* (2003)

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.

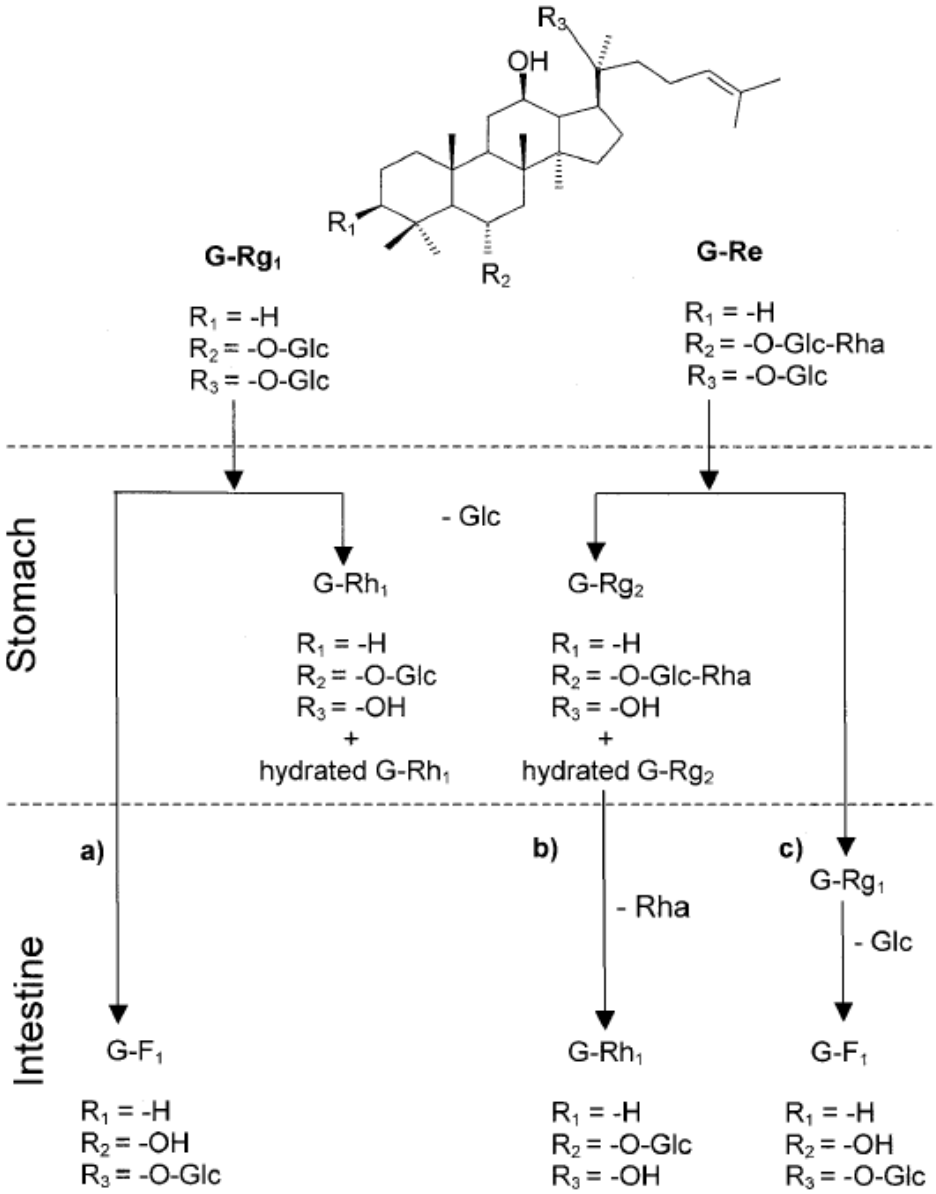


Fig.3: Tawab *et al.* (2003): Possible degradation pathway of ginsenosides Rg_1 and Re

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 (Table 5) but were not assessed, since the description of the preparations is considered not sufficient.

Table 5: Overview of clinical studies on ginseng preparations not assessed (insufficient characterisation of the herbal preparation)

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
Ong Lai Teik D et al. (2016)	Panax ginseng extract, standardized to 3% ginsenosides, no information on DER and extraction solvent
Shah SA et al. (2016)	Panax ginseng, no further information
Jung DH et al. (2016)	Korean red ginseng, characterisation of ginsenosides but no information if extract or powdered herbal drug
Jovanovski E et al. (2014a)	Korean red ginseng extract enriched in Rg_3, extraction solvent 50 and 80 % ethanol, followed by enzyme and acid hydrolysis, no information on DER
Jovanovski E eta l (2014b)	Korean red ginseng rootlets extract, no information on extraction solvent and DER
Park K et al. (2020)	Korean red ginseng extract, no information on extraction solvent and DER
Seo SK et al. (2014)	Korean red ginseng, no further information
Ghorbani Z et al. (2019)	Panax ginseng, no further information
Chung YS et al. (2021)	Korean red ginseng, no further information
Kim IK et al. (2021)	Korean red ginseng, 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.* (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.

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.

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.

Cha TW *et al*. (2016)

The effects of red ginseng consumption on blood pressure (BP) and the fasting plasma metabolome were investigated in a randomized, double-blind, placebo-controlled study. Nonobese, nondiabetic, prehypertensive subjects were included and daily received 5 g red ginseng (n=31) or placebo (n=31). Fasting plasma metabolome profiles were obtained using ultra performance liquid chromatography-linear trap quadrupole Orbitrap MS. After 12 weeks, participants consuming red ginseng showed reductions of 6.5 and 5.0 mm Hg in systolic and diastolic BP, respectively. Compared with controls, those consuming red ginseng showed greater reductions in changed values of systolic BP, diastolic BP and lipoprotein-associated phospholipase A2 (Lp-PLA2) activity, after adjusting for baseline values. In addition, the red ginseng group showed a greater increase in dihydrobiopterin levels and greater decrease in palmitic amide and lysophosphatidylcholines (lysoPCs). The change in diastolic BP positively correlated with changes in lysoPCs and Lp-PLA2 activity. According to the authors, the BP-lowering effect of red ginseng is associated with decreased Lp-PLA2 and lysoPCs and increased dihydrobiopterin levels in prehypertensive subjects.

Park KS *et al.* (2014)

A randomized double-blind, placebo-controlled trial on Korean red ginseng (KRG) was conducted in order to investigate its potential effect on on cold hypersensitivity in the hands and feet (CHHF), a common complaint among Asians, especially women. The study included 80 female patients with CHHF at Kyung Hee University Hospital at Gangdong, Seoul, Korea. The participants took six capsules of 500-mg KRG powder or placebo twice daily for 8 weeks and were followed up for 4 weeks. The primary outcome measure was change in skin temperature of the hands. The secondary outcome measures

included change in skin temperature of the feet, visual analog scale (VAS) scores of CHHF severity, recovered temperature (RT) of the hands after cold stress test, distal-dorsal difference (DDD) in temperature of the hands, power variables of heart rate variability (HRV), and 36-item Short-Form Health Survey (SF-36) scores. The KRG group had significantly higher skin temperature of the hands and feet, lower VAS scores, higher RT of the right 5th finger, and less parasympathetic activity than the placebo group at 8 weeks. No significant differences were noted in DDD of the hands and SF-36 scores. No serious adverse events were reported during the study. The authors concluded that peripheral vasodilation by KRG may alleviate CHHF and that further controlled studies are required to elucidate the effects of KRG on the autonomic nervous system.

Kwon YJ *et al.* (2020)

The aim of this pilot study was to investigate the effect of KRG on cholesterol metabolites, which are surrogate markers of cholesterol absorption and biosynthesis, in postmenopausal women with hypercholesterolemia. The present study is an exploratory study which used data from a 4-week, double-blinded, placebo-controlled clinical pilot study in 68 postmenopausal women with hypercholesterolemia. Patients received KRG (2 g) or placebo (2 g) once daily. The primary endpoints were changes in the levels of nine sterols. Serum sterols were analysed using liquid chromatography-mass spectrometry (LC-MS)/MS analysis. According to the authors, among the sterols, reduction in cholesterol level were significantly larger in the KRG group than in the placebo group (the changes: -148.3 ± 261.1 nmol/mL in the ginseng group vs. -23.0 ± 220.5 nmol/mL in the placebo group, p = 0.039). Additionally, changes in 7-hydroxycholesterol (7-OHC) were significantly larger in the KRG group than in the placebo group (the changes: -0.05 ± 0.09 nmol/mL in the ginseng group vs. -0.002 ± 0.1 nmol/mL in the placebo group, p = 0.047). The authors concluded that KRG improved sterol metabolism by decreasing cholesterol and 7-OHC levels in postmenopausal women with hypercholesterolemia.

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.

Yang M *et al.* (2014)

In this single-blind randomized clinical trial, the efficacy and safety outcomes of KRG against BPA, focusing on female quality of life (QOL) was investigated. Individual variations in susceptibility to KRG were also investigated with the Sasang Typology, the personalized medicine used for hundred years in Korea. Study subjects were young women (N = 22), consumed 2.7 g of KRG or placebo per day for 2

weeks and filled up questionnaires regarding gynecologic complaints at the 4 time spots. Urinary total BPA and malondialdehyde (MDA), an oxidative stress biomarker, were examined with GC/MS and HPLC/UVD respectively. Furthermore, their Sasang Typology was diagnosed with the questionnaire for the Sasang constitution Classification (QSCC II). KRG consumption decreased urinary BPA and MDA levels (ps < 0.05) and alleviated 'menstrual irregularity', 'menstrual pain', and 'constipation' (ps < 0.05). SoEum type (Lesser Yin person) among the Sasang types showed significant alleviation in insomnia, flushing, perspiration and appetite by KRG consumption, rather than other Sasang types. During the intervention, no one experienced any aggravated side effects. The authors concluded that KRG is efficient for protection for female QOL and BPA- exposure and - related oxidative stress. However, individual variation in susceptibility to KRG should be further considered for identifying ideal therapy.

Kim HS *et al.* (2017)

The effects of red ginseng on toxicity, health-related quality of life (HRQL) and survival after adjuvant chemotherapy in patients with epithelial ovarian cancer (EOC) were studied. A total of 30 patients with EOC were randomly assigned to placebo (n = 15) and red ginseng groups (n = 15). All patients took placebo or red ginseng (3000 mg/day) for three months. Then, changes of genotoxicity, HRQL and survival were compared between the two groups. According to the authors, red ginseng reduced micronuclei yield in comparison with placebo despite no difference of binucleated cells index. Although red ginseng increased serum levels of alanine aminotransferase and aspartate aminotransferase significantly, they were within the normal value. Moreover, there were no differences in adverse events between placebo and red ginseng groups. In terms of HRQL, the authors stated that red ginseng was associated with improved emotional functioning and decreased symptoms of fatigue, nausea and vomiting, and dyspnea, reduced anxiety and interference affecting life and improved daytime somnolence. However, there was no effect of red ginseng on prognosis of EOC. The authors concluded that red ginseng was safe and effective to reduce genotoxicity and improve HRQL despite no benefit of survival in patients with EOC who received chemotherapy was seen.

Effects on chronic fatigue (CRF)

Sung WS *et al.* (2020)

The purpose of this study was to investigate the effect of KRG on chronic fatigue (CF) by various measurements and objective indicators. A randomized, double-blind, clinical trial was conducted on 50 patients with CF. Participants were allocated to KRG or placebo group (1:1 ratio) and visited hospital every 2 weeks during taking 3 g KRG or placebo for 6 weeks and followed up 4 weeks after the treatment. The primary outcome measurement was fatigue VAS. Secondary outcome measurements included FSS, CFSQ, SRI, scales of various fields (Depression: BDI; Sleep: ISI; Quality of life: EQ-5D 5 L), biochemical test (Antioxidants: d-ROMs, TBARS, BAP, and SOD; Cortisol concentration: salivary cortisol), blinding assessment, and adverse events. The fatigue VAS declined significantly in each group, but there were no significant differences between the groups. The 2 groups also had no significant differences in the secondary outcome measurements and there were no adverse events. Sub-group analysis indicated that patients with initial fatigue VAS below 80 mm and older than 50 years had significantly greater reductions in the fatigue VAS if they used KRG rather than placebo. The authors concluded that KRG did not show absolute anti-fatigue effect. However, the therapeutic potential for middle-aged individuals with moderate fatigue could be explored.

Kim JW *et al.* (2020)

For this randomised and double-blinded trial, colorectal cancer patients who received mFOLFOX-6 were randomly assigned to either KRG 2000 mg/day (n = 219) or placebo (n = 219) for 16 weeks. CRF was

evaluated using the mean area under the curve (AUC) change from baseline of brief fatigue inventory (BFI) as the primary endpoint. Fatigue-related quality of life, stress, and adverse events were evaluated as secondary endpoints. In the full analysis group, KRG up to 16 weeks improved CRF by the mean AUC change from baseline of BFI compared to placebo, particularly in "Mood" and "Walking ability" (P = 0.038, P = 0.023, respectively). In the per-protocol group, KRG led to improved CRF in the global BFI score compared with the placebo (P = 0.019). Specifically, there were improvements in "Fatigue right now," "Mood," "Relations with others," "Walking ability," and "Enjoyment of life" at 16 weeks (P = 0.045, P = 0.006, P = 0.028, P = 0.003, P = 0.036, respectively). In subgroups of female patients, ≥60 years old, with high compliance (≥80%) or more baseline fatigue, the beneficial effects of KRG were more enhanced than that of placebo. Although neutropenia was more frequent in KRG than placebo, the incidence of all adverse events was similar. The authors concluded that KRG could be safely combined with mFOLFOX-6 chemotherapy in colorectal cancer patients, and reduced CRF compared with placebo.

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 leucocyte 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.

Scaglione *et al.* 2005 (Review on G115)

Scaglione *et al*. reviewed the properties and usage of the standardized *Panax ginseng* C.A. Mey., radix 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.

Further relevant clinical studies on G115:

Cognition and cerebrovascular function:

Reay *et al.* (2010)

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.

Reay *et al.* (2008)

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:

Shergis JL *et al.* (2019)

In a multicentre, randomised, double-blind, placebo-controlled trial safety and efficacy in patients with moderate COPD were investigated. During 24 weeks ginseng capsules (G 115, 100 mg twice daily) were compared with placebo. Participants were followed up for a further 24 weeks. Participants were aged 40 years and over and had airflow limitation in the moderate (Global Initiative for Chronic Obstructive Lung Disease 2) COPD range. The coprimary endpoints were the St George's Respiratory Questionnaire, the COPD Assessment Test and the Short Form Health Survey. Secondary outcomes included lung function, exacerbation rate and use of relief medication. 168 participants were randomised 1:1 from five centres in Australia and China. Baseline characteristics were balanced between groups. There were no significant differences between ginseng and placebo, with overall results improving in both groups. Ginseng seemed safe for, and well tolerated by, people with COPD. However, there was no significant difference in improvement in health-related quality of life (primary outcome) between the ginseng and placebo groups.

TRIAL REGISTRATION NUMBER: ACTRN12610000768099.

Assessor's comment:

Shergis JL et al. published the results of the study included in the previous assessment report under the reference Xue et al. (2011).

Chen Y *et al.* (2020)

This study evaluated the therapeutic value of ginseng capsules in reducing acute exacerbations and improving the quality of life in people with COPD. In a randomized, double-blind and placebo-controlled trial ginseng's effects on 200 patients with moderate to very severe COPD was investigated. Ginseng capsules (G 115, 200 mg, twice per day) were compared to placebo over 24 weeks. Patients were followed up for a further 24 weeks after the treatment period. The primary outcome measure was acute COPD exacerbation rate over 12 months. Secondary outcome measures were health-related quality of life, including the St George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT) and the Short Form 36 Health Survey (SF-36). Furthermore, lung function, walking distance and use of relief medication was assessed. Baseline characteristics were balanced between groups. The rate of COPD exacerbations was not statistically significant between groups after 1 year (62 participants in the ginseng group and 63 in the placebo group). Secondary outcome measures showed improvements after ginseng and placebo but results were not clinically significant. The incidence of adverse events in the two groups was similar and events were unrelated to the intervention. The authors concluded that, compared with placebo, ginseng did not reduce the rate of acute COPD exacerbations over 12 months. However, the preparation was safe and well tolerated by people with moderate to very severe COPD.

Gross *et al.* (2002)

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 treatmenthas 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:

Cardinal & Engels (2001)

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 behavioural 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.

Other herbal preparations:

Yennurajalingam S e*t al.* (2017)

The primary objective of this study was to compare the effects of oral Panax ginseng extract (extraction solvent ethanol 70%, DER 1:3-5, then standardized to contain ≥7.0% of ginsenosides and malonyl ginsenosides) and placebo on CRF. Secondary objectives were to determine the effects of PG on QoL, mood, and function. In this randomized, double-blind, placebo-controlled study, patients with CRF ≥4/10 on the Edmonton Symptom Assessment System (ESAS) were eligible. Based on a pilot study, patients were randomized to receive either 400 mg of standardized PG twice daily or a matching placebo for 28 days. The primary end point was change in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale from baseline to day 29. Of 127 patients, 112 (88.2%) were evaluable. The mean (SD) FACIT-F subscale scores at baseline, day 15, and day 29 were 22.4 (10.1), 29.9 (10.6), and 30.1 (11.6) for PG (P<.001), and 24.0 (9.4), 30.0 (10.1), and 30.4 (11.5) for placebo (P<.001). Mean (SD) improvement in the FACIT-F subscale at day 29 was not significantly different in the PG than in the placebo group (7.5 [12.7] vs 6.5 [9.9]; P=.67). QoL, anxiety, depression, symptoms, and functional scores were not significantly different between the PG and placebo groups. Improvement in the FACIT-F subscale correlated with baseline scores (P=.0005), Hospital Anxiety and Depression Scale results (P=.032), and sex (P=.023). There were fewer any-grade toxicities in the PG versus placebo group (28/63 vs 33/64; P=.024). The authors concluded that both PG and placebo resulted in significant improvement in CRF. PG was not significantly superior to placebo after 4 weeks of treatment.

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 6**.

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.

Safety:

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 6 Overview of clinical studies included in the systematic review by Lee & Son (2011)

Reference	Jadad score	Design	Participants and sample size	Intervention/control (dosage)	Primary endpoint	Main results according to the authors	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 weeks	Effect on aerobic, anaerobic performance, central and peripheral fatigue	No significant effects	Not described
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	Crossov er	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	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 g)/placebo for 4 weeks	Effects on electrocardiograph	Increased QTc interval, decreased diastolic blood pressure	One case of nausea and vomiting
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.

Physical performance:

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 7**.

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 7**.

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 7**.

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 7: Overview of clinical studies included in the systematic review by Vogler *et al.* (1999)

Reference	Jadad score	Design	Participants and sample size (ginseng/control) age in years	Intervention/control (dosage)	Primary endpoint	Main results according to the authors	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 flavonglycoside and 7.2 mg terpenlactone daily)/vitamins /placebo for 3 months	Concentration test, selective memory test	Selective memory significantly improved compared with placebo (P<0.02)	Not reported
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

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 available). 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.

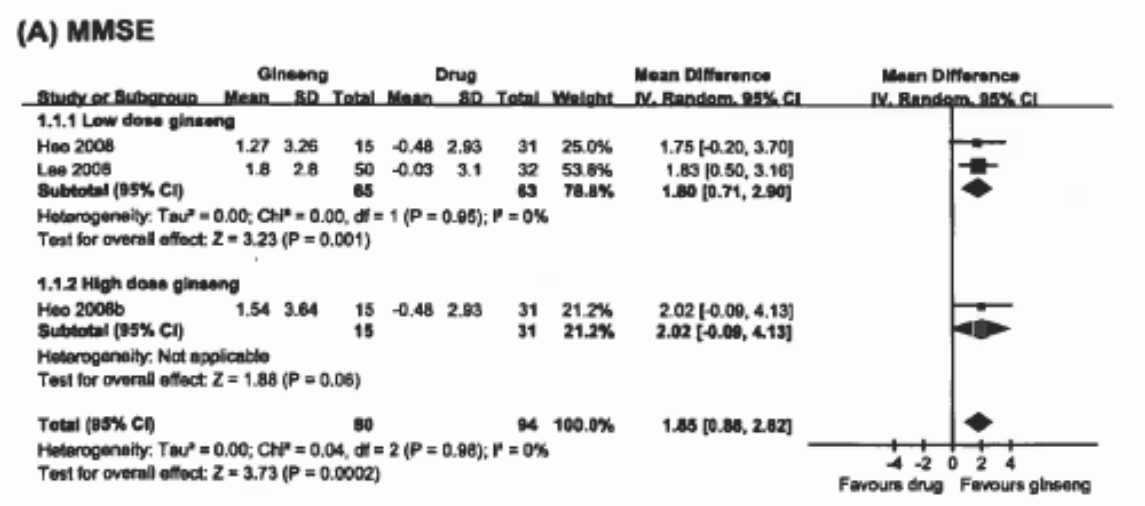
Lee MS *et al*. (2009): Ginseng for Cognitive function in Alzheimer's Disease: A systematic review

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).

Outcomes:

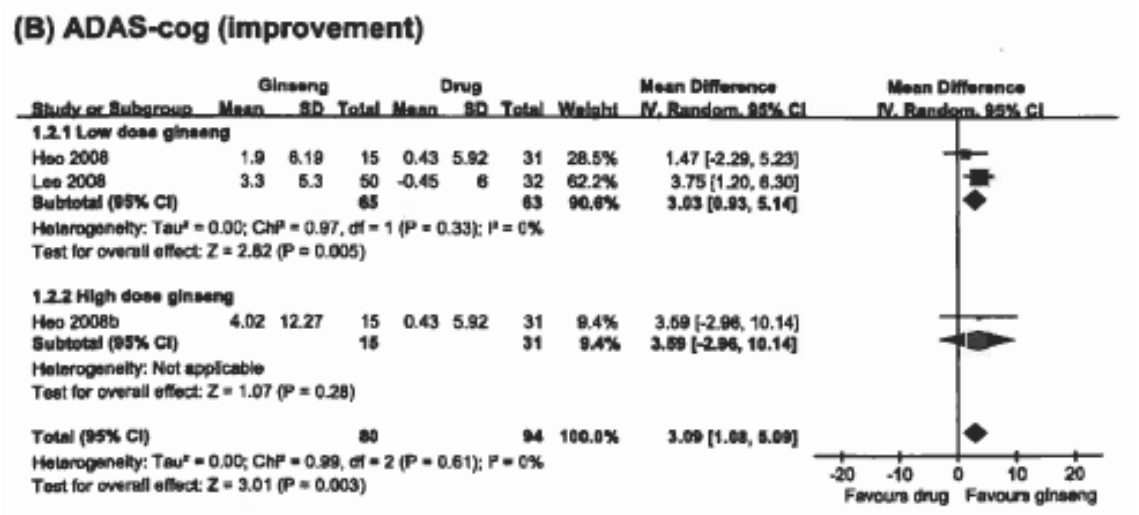
MMSE: High dosages of red ginseng (9 g/day) significantly improved MMSE compared with conventional therapy after 12 weeks while a low dose of red ginseng (4.5 g/day) failed to do so. Low dose of white ginseng (4.5 g/day) showed favourable effects compared with standard drug therapy after 4 weeks and 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



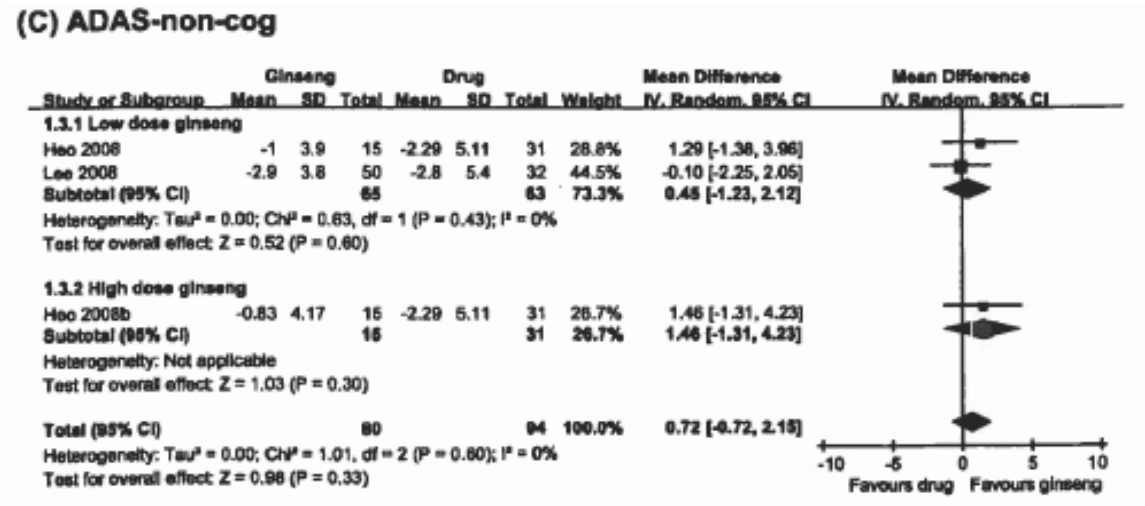
ADAS cognitive function: One RCT showed significant effects of white ginseng on ADAS-cognitive subscale after 4 and 12 weeks. The other RCT failed to do so for red ginseng. The meta-analysis of the RCTs suggested ginseng plus conventional drugs to be superior to conventional drugs alone in improvement 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 of 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.

Effects on blood pressure:

Twelve studies included blood pressure outcomes, most evaluated *Panax ginseng* preparations

(5 monos, see **Table 8**). 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 8: Short description of studies evaluating effects of *Panax ginseng* monopreparations on blood pressure included in the systematic review by Buettner *et al.* (2006)

Reference	Design / Jadad	Subjects (mean age, y)	Ginseng dose (% ginsenoside)/ Manufacturer/duration of treatment	Effect change according to the authors
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

Effects on cholesterol:

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 9**). 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 9: Short description of studies evaluating effects of *Panax ginseng* monopreparations on blood lipids included in the systematic review by Buettner *et al.* (2006)

Reference	Design/ Jadad score	Subjects (mean age, y)	Ginseng dose (% ginsenoside)/ Manufacturer/duration of	Effect change according to the authors
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

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 10**), 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 10: Short description of studies evaluating effects of *Panax ginseng* monopreparations on blood glucose included in the systematic review by Buettner *et al.* (2006)

Reference	Design/ Jadad score	Subjects (mean age, y)	Ginseng dose (% ginsenoside)/ Manufacturer/duration of treatment	Effect change (according to the authors)
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)

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.

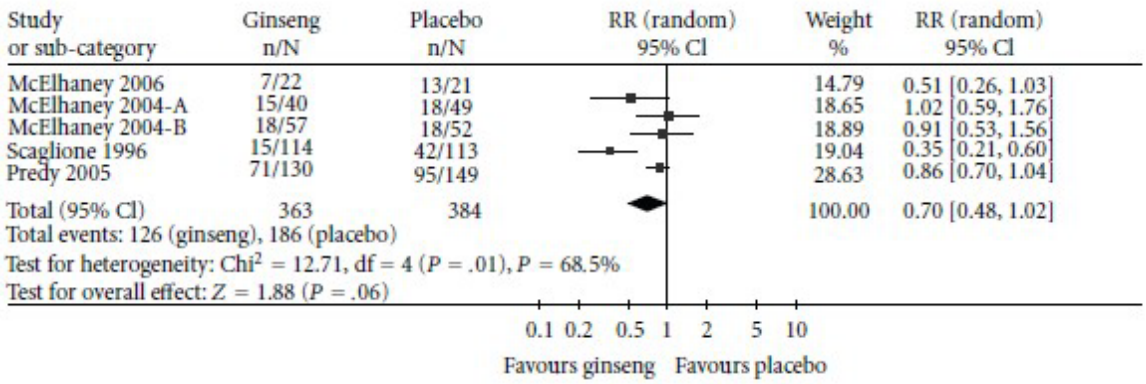


Fig. 7: Forest-plot of incidence of having at least one cold or (in Krebs Seida *et al.* (2011)) acute respiratory infection

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 11**.

Table 11Overview of clinical studies included in the systematic review by Jang *et al.* (2008)

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.

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**.

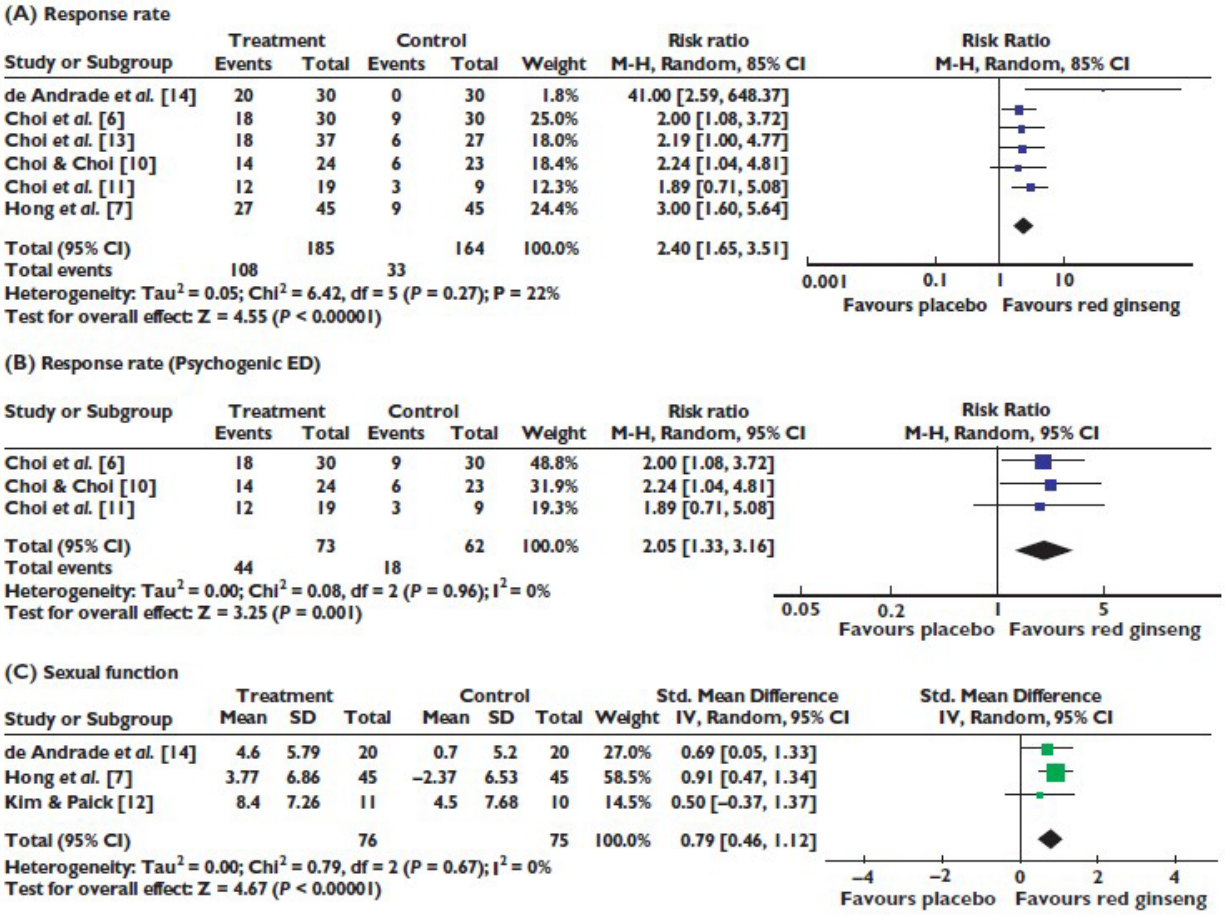


Fig. 8: Forest plot of red ginseng for ED on response effectiveness in all kinds of ED (A), psychogenic ED (B) and on sexual function on questionnaires (C); ED erectile dysfunction; IIEF: International Index of Erectile function

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.

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

No specific data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

Numerous clinical studies on ginseng preparations, especially on powdered white (herbal preparation b) and red ginseng (herbal preparation k), and the extract G115 (herbal 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 gynaecology, on fatigue/cancer related fatigue, 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.

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.

Mastalgia, vaginal bleeding and gynaecomastia:

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.

Diuretic resistance:

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)

Stevens-Johnson Syndrome:

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.

Psychiatric conditions:

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)

Cerebral arteritis:

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)

Agranulocytosis:

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)

Eye symptoms:

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).

Hypertension:

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.

Epidemiological studies:

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.

Data from Ginseng manufacturers

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.

Information from Eudravigilance database:

77 results concerning Ginseng have been identified by 13 July 2021. In the majority of cases the herbal preparation is not clearly defined (usually just "ginseng" or "panax ginseng" is mentioned). Also reports related to Panax quinquefolius and Eleutherococcus senticosus were included, which are not relevant for the monograph on Panax ginseng. Several reports are related to combination products, or patients used concomitant medication, which makes it impossible to establish a clear correlation or even causality. Case reports from literature references are rather general, referring to "herbal supplements" or "complementary medicine", clear correlation or even causality cannot not be established. Suspected interactions are in the majority of cases based on single case reports or related to patients with co-medication of a considerable amount of different chemical/biological drug substances. Overall, few cases are related to authorised medicinal products, the reported adverse events (such as gastrointestinal disorders, urticaria, itching, night sweat, restlessness) are included in section 4.8 of the monograph.

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.

Aside from market presence and data from studies, there are no concrete data concerning patient exposure.

5.3. Adverse events, serious adverse events and deaths

See also 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

5.5.1. Use in children and adolescents

One clinical trial on the effect of red ginseng on ADHD in children (6-15 years, n=70) has been found. Children with ADHD symptoms received either one pouch (40 ml) of Korean red ginseng extract (1g of KRG concentrated extract) twice a day or placebo. According to the authors the red ginseng group had significantly decreased inattention/hyperactivity scores compared with the control group at the 8 week point. No serious adverse events were reported in either group. (Ko *et al*. 2014).

Assessor's comment:

Although the herbal preparation was well tolerated, the study is considered too small to conclude on a general safety of red ginseng in children. Moreover, the herbal preparation is not sufficiently characterised ('Korean red ginseng extract', no further information).

5.5.2. Contraindications

Hypersensitivity to the active substance (see 5.3)

5.5.3. Special warnings and precautions for use

The use in children and adolescents under 18 years of age has not been established due to lack of adequated data.

5.5.4. Drug interactions and other forms of interaction

Impact on CYP 450 - Drug interactions

Anderson *et al.* (2003)
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.

Gurley *et al.* (2005, abstract only)

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 pre-treatment 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 ofINR 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.

Choi MK & Song IS (2019)

This review comprehensively discusses drug metabolizing enzyme- and transporter-mediated ginseng-drug interaction by analysing in vitro and clinical results with a focus on ginsenoside, a pharmacologically active marker of ginseng. Impact of ginseng therapy or ginseng combination therapy on diabetic patients and of ginseng interaction with antiplatelets and anticoagulants were evaluated based on ginseng origin and ginsenoside content. Daily administration of Korean red ginseng (0.5-3 g extract; dried ginseng > 60%) did not cause significant herb-drug interaction with drug metabolizing enzymes and transporters. Among various therapeutic drugs administered in combination with ginseng, adjuvant chemotherapy, comprising ginseng (1-3 g extract) and anticancer drugs, was effective for reducing cancer-related fatigue and improving the quality of life and emotional scores. Limited information regarding ginsenoside content in each ginseng product and plasma ginsenoside concentration among patients necessitates standardization of ginseng product and establishment of pharmacokinetic-pharmacodynamic correlation to further understand beneficial effects of ginseng-therapeutic drug interactions in future clinical studies.

Lim JW et al. (2018)

The authors discussed herbs that have potential interactions by exploring Western and TCM approaches to thrombotic events, among them also P. ginseng. They conclude, that various in vitro studies have demonstrated that ginseng inhibits several steps along the platelet aggregation pathway, as well as the coagulation cascade, suggesting that pharmacodynamic interactions with aspirin may be possible. On the whole, despite laboratory evidence of inhibited platelet aggregation by Asian ginseng, clinical evidence indicates that there is little cause for concern regarding increased bleeding risk, and hence pharmacodynamic interactions, when Asian ginseng is taken with aspirin. Pharmacokinetic interactions have also not been reported

Ramanathan MR & Penzak SR (2017)

The authors reported that numerous preclinical studies have assessed the influence of various ginseng components on cytochrome P450 (CYP), glucuronidation, and drug transport activity. Results from these investigations have been largely inconclusive due to the use of different ginseng products and variations in methodology between studies. Drug interaction studies in humans have been conflicting and have largely yielded negative results or results that suggest only a weak interaction. One study using a midazolam probe found weak CYP3A induction and another using a fexofenadine probe found weak P-gp inhibition. Despite several case reports indicating a drug interaction between warfarin and P. ginseng, pharmacokinetic studies involving these agents in combination have failed to find significant pharmacokinetic or pharmacodynamic interactions. The authors concluded that to this end, drug interactions involving P. ginseng appear to be rare; however, close clinical monitoring is still suggested for patients taking warfarin or CYP3A or P-gp substrates with narrow therapeutic indices.

Chua YT et al. (2015)

The authors aim was to raise awareness about potential interactions between herbs used in TCM and warfarin, a drug that is especially susceptible to herb-drug interactions due to its narrow therapeutic range. Among other medicinal plants also P. ginseng was assessed. The authors concluded that The effect of ginseng on warfarin has not been established due to abundant conflicting results. Ginseng has been associated with a few episodes of spontaneous bleeding, but have also been associated with

reports of subtherapeutic INR and thrombosis in patients previously stable on warfarin. The effect of ginseng on warfarin has not been replicated in clinical trials. A randomised, open-label, controlled study of newly diagnosed ischaemic stroke patients (n = 35) found that two weeks of concomitant use of Panax ginseng extract (1.5 g) with warfarin did not significantly affect peak values, INR and PT area under the curve, thus concluding that Panax ginseng did not influence the pharmacological action of warfarin.

Fung FY *et al.* (2017)

In a randomized, double-blind, placebo-controlled trial, among other herbal preparations, also *Panax ginseng* was investigated for anti-platelet and anticoagulation effects, alone and in combination with aspirin. 25 healthy volunteers were included for each herbal preparation. Each subject underwent 3 phases comprising of herbal product (2x 500 mg/day of powdered white ginseng) alone, aspirin alone and aspirin with herbal product, where each phase lasted for 3 weeks with 2 weeks of washout between phases. PT/APTT, platelet function by light transmission aggregometry and thrombin generation assay by calibrated automated thrombogram were measured at baseline and after each phase. Information on adverse reaction including bleeding manifestations was collected after each phase. Overall, there was no clinically relevant impact on platelet and coagulation function. 1 of 23 subjects in the Panax ginseng group had an inhibition in arachidonic-acid induced platelet aggregation. Combination of these herbal products with aspirin respectively did not further aggravate platelet inhibition caused by aspirin. None of the herbs impaired PT/APTT or thrombin generation. There was no significant bleeding manifestation. The authors concluded that this study on healthy volunteers provided good evidence on the lack of bleeding risks of the investigated herbal preparations either used alone or in combination with aspirin.

Seong SJ et al. (2018)

In an open-label, randomized, 3-period study investigated the in vivo herb-drug interaction potential for red ginseng extract with cytochrome P-450 (CYP) enzymes and organic anion-transporting polypeptide (OATP) 1B1. Fifteen healthy male volunteers (22-28 years; 57.1-80.8 kg) were administered a single dose of cocktail probe substrates (caffeine 100 mg, losartan 50 mg, omeprazole 20 mg, dextromethorphan 30 mg, midazolam 2 mg, and pitavastatin 2 mg) and single or multiple doses of red ginseng extract for 15 days. The pharmacokinetic profiles of the probe substrates and metabolites after single- or multiple-dose administration of red ginseng extracts were comparable to the corresponding profiles of the control group. The geometric mean ratio of AUC0-t and 90% CIs for the probe substrate drugs between the control and multiple doses of red ginseng for 15 days were within 0.8 to 1.25 (CYP2C9, CYP3A4, and OATP1B1 probe substrates) or slightly higher (CYP1A2, CYP2C19, and CYP2D6 probe substrates). Additional assessments of the in vitro drug interaction potential of red ginseng extracts and the ginsenoside Rb1 on drug-metabolizing enzymes and transporters using human liver microsomes, cryopreserved human hepatocytes, and transporter-overexpressed cells were negative. The authors concluded that red ginseng poses minimal risks for clinically relevant CYP- or OATP-mediated drug interactions and was well tolerated.

Calderón MM et al. (2014)

The purpose of this study (single-sequence, open-label, single-center pharmacokinetic investigation) was to determine the influence of P. ginseng on the pharmacokinetics of the HIV protease inhibitor combination lopinavir-ritonavir (LPV-r) in healthy volunteers. Twelve healthy volunteers received LPV-r (400-100 mg) twice/day for 29.5 days. On day 15 of LPV-r administration, serial blood samples were collected over 12 hours for determination of lopinavir and ritonavir concentrations. On study day 16, subjects began taking P. ginseng 500 mg twice/day, which they continued for 2 weeks in

combination with LPV-r. On day 30 of LPV-r administration, serial blood samples were again collected over 12 hours for determination of lopinavir and ritonavir concentrations. Lopinavir and ritonavir pharmacokinetic parameter values were determined using noncompartmental methods, and pre administration and post administration ginseng values were compared using a Student t test, where $p<0.05$ was accepted as statistically significant. Neither lopinavir nor ritonavir steady-state pharmacokinetics were altered by 2 weeks of P. ginseng administration to healthy human volunteers. Thus, the authors concluded that a clinically significant interaction between P. ginseng and LPV-r is unlikely to occur in HIV-infected patients who choose to take these agents concurrently. It is also unlikely that P. ginseng will interact with other ritonavir-boosted protease inhibitor combinations, although confirmatory data are necessary.

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.

In course of the literature search during revision 1, a considerable number of studies applying in vitro as well as in vivo animal models in order to investigate herb-drug interactions related to P. ginseng preparations has been found [Kim Y et al. (2020), Abushammala IM et al. (2021),Lin JF et al. (2020), Sun H et al. (2016), Ryu SH et al. (2014), Dong H et al. (2017), Li N et al. (2014)] . In addition, few publications on clinical data from drug interaction studies related to P. ginseng have been found (please refer to summaries above). Furthermore, several 'general reviews' of interactions between traditional herbal medicines and chemical active substances have been published [Petersen M et al. (2021), Ratan ZA et al. (2021), Fasinu PS et al. (2015), Milić N et al. (2014)]. In the majority of publications, the herbal preparation is not sufficiently characterised or rather high doses of isolated ginsenosides or 'extracts' are used in vitro or in animal models. Overall, although there are several hints from in vitro data that interactions with Warfarin, and CYP 3A or P-gp substrates could be possible, so far available clinical data does not confirm these findings.

5.5.5. Fertility, pregnancy and lactation

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.

5.5.6. Overdose

See section 5.5.8

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

One RCT on the effect of a single dose of 1200 mg of ginseng on the ability to drive and use machines has been found. The 30 volunteers were randomized into three groups of ten subjects per group (placebo, ginseng, ginkgo). There was no statistically significant difference between ginseng and placebo. According to the authors no final conclusions can be drawn as the study is rather small. (La Sala et al., Clin Toxicol (Phila). 2015 Feb;53(2):108-12.)

Assessor's comment:

Besides the small number of participants in the study, the herbal preparation is not sufficiently characterised (combination of P. ginseng root extract and ginsenosides, no further information).

5.5.8. Safety in other special 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.

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 (benefit-risk assessment)

The underground parts of *Panax ginseng* C.A. Mey., radix 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 European Union 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. No constituent with known therapeutic activity or active marker can be recognised by the HMPC. Typical analytical markers are the ginsenosideds. Nevertheless, thirteen herbal preparations (a-m, 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.

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.

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 European Union list entry is not proposed.

Annex

List of references