25 March 2014
EMA/HMPC/680615/2013
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim., radix

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim., radix
Herbal preparation(s)	Comminuted herbal substance Powdered herbal substance Liquid extract (DER 1:1, extraction solvent ethanol 30-40% v/v) Dry extract (DER 13-25 : 1, extraction solvent ethanol 28-40% v/v) Dry extract (DER 17-30 : 1, extraction solvent ethanol 70% v/v) Dry aqueous extract (DER 15-17:1) Tincture (ratio of herbal substance to extraction solvent 1:5, extraction solvent ethanol 40% v/v) Liquid extract (DER 1:11), extraction solvent sweet wine Liquid extract (DER 1:20), extraction solvent sweet wine
Pharmaceutical forms	Comminuted herbal substance as herbal tea for oral use Herbal preparations in solid or liquid dosage forms for oral use.
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Table of contents

1. Introduction

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

- **Herbal substance(s)**

Eleutherococcus root (Eleutherococci root) is a dried, whole or cut underground organs of *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim. with a content of a minimum 0.08% for the sum of eleutheroside B and eleutheroside E (European Pharmacopoeiea, 2013).

The correct binomial botanic name is *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim., syn. Acanthopanax senticosus (Rupr. et Maxim.) Harms. Eleutherococcus was formerly known as Acanthopanax senticosus (Rupr. et Maxim.) Harms and this name is still widely used by Chinese scientists (Li *et al.,* 2005; Frodin, 2006).

The first English name, created in the USA for Eleutherococcus, was “Eleuthero” (Baranov, 1979). "Siberian Ginseng" has been used in the USA as a second name since 1971, but the name has been banned by the Ginseng Labelling Act of 2002 (Farnsworth *et al.,* 1986; Israelsen, 1993). Fifteen names that are based on the abbreviated Latin generic name “Eleuthero” are currently used in various EU official languages; in 4 languages variants from name “Siberian Ginseng”, in 4 languages – variants from “Russian root” or “Russian ginseng root”, and in German and in Hungarian variants from “Taiga root” - “Taigawurzel” and “tajga gyökér” are used.

In this assessment report the names “Eleutherococcus” or latin “*Eleutherococcus senticosus*” are used although both synonyms may be found in the original articles.

Constituents

Although over 35 compounds have been identified from the Eleutherococcus root, the search for active substances is not finished yet. *Eleutherococcus senticosus* is characterised by the co-existence of pentacyclic and tetracyclic triterpenoidal saponins and their prosapogenins, lignans, coumarins, phenylcarbonic acids and xanthones (Jeljakov *et al.,* 1972; Sandberg, 1973; Anetai *et al.,* 1987; Sonnenborn *et al.,* 1993; Deyama *et al.,* 2001).

The main constituents are:

- phenyl propane compounds: eleutheroside B (or syringin) – 0.5% (Ovodov *et al.,* 1967), chlorogenic acid – up to 0.3% (Deyama *et al.,* 2001), coniferyl aldehyde and its glucoside (Deyama *et al.,* 2001), caffeic acid derivates (Wagner *et al.,* 1982; Liu *et al.* 2012a);
- lignanes: (+)-syringaresinol –O-β-D-glucoside (or eleutheroside E) – 0.1% (Ovodov *et al.,* 1967; Deyama *et al.,* 2001), episyringaresinol-4’’-O-β-D-glucoside (or Eleutheroside E_2) (Li *et al.,* 2001), ((-)-sesamin (or eleutheroside B_4) – 0.023% (Suprunov *et al.,* 1971; Bladt *et al.,* 1990; Li *et al.,* 2001), (-)-Syringaresinol-4-4’-O-β-D-diglucosid (or Eleutherosid D) – 0.10%, (Ovodov *et al.,* 1967) , (-)-Syringaresinol-4-O-β-D-monoglucosid (or Eleutherosid E_1) (Aicher *et al.,* 2006, 2012), (-)-Syringaresinol (Aicher *et al.,* 2006, 2012); (+)-pinoresinol di-O- β-D-glucoside (Deyama *et al.,* 2001);
- coumarins: isofraxidin (6,8-dimethoxy-7-hydroxycumarin) (Wagner *et al.,* 1982; Deyama *et al.,* 2001) and its O-glucoside eleutherosid B_1 (Nörr, 1993; Deyama *et al.,* 2001), 7-ethyl-umbelliferone (Barnes *et al.,* 2007).

- triterpensaponines: daucosterol (eleutheroside A), β -hederin (Eleutheroside K) (Farnsworth *et al.,* 1985),2-protoprimulagenin A-glycoside – 0.125% (Segiet-Kujawa *et al.,* 1991; Evans *et al.,* 2002).
- polysaccharides (heteroglycans and eleutherans) (Fang *et al.,* 1985; Wagner *et al.,* 1984; Wagner *et al.,* 1985; Shen *et al.,* 1991).

Other constituents comprise steroids, carbohydrates and essential oil 0.8% (Barnes *et al.,* 2007).

- **Herbal preparation(s)**
  - Comminuted herbal substance
  - Powdered herbal substance
  - Liquid extract (DER 1:1, extraction solvent ethanol 30-40% v/v)
  - Dry extract (DER 13-25 : 1, extraction solvent ethanol 28-40% v/v)
  - Dry extract (DER 17-30 : 1, extraction solvent ethanol 70%, v/v)
  - Dry aqueous extract (DER 15-17:1)
  - Tincture (ratio of herbal substance to extraction solvent 1:5, extraction solvent ethanol 40% v/v)
  - Liquid extract (DER 1:11), extraction solvent sweet wine
  - Liquid extract (DER 1:20), extraction solvent sweet wine

- **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.**

Eleutherococcus root and extracts are used in combinations with other herbal substances/herbal preparations (e.g. *Rhodiola rosea* L., root; *Leuzea carthamoides* (Willd.) D.C., root; *Schizandra chinensis* (Turcz.) Baill., fructus *Andrographis paniculata,* herba etc.). Such combinations have not been assessed. This assessment report refers exclusively to Eleutherococcus root and preparations thereof.

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

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify: Food supplements	No medicinal products
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify: Food supplements	
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Two medicinal products
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	One medicinal product
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Ten medicinal products
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify: Food supplements	No medicinal products
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	One medicinal product
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products, no food supplements
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	One medicinal product
Sweden	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	One medicinal product
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

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

1.3. Search and assessment methodology

Databases and other sources used to research available pharmaceutical, non-clinical and clinical data on *Eleutherococcus senticosus* or its relevant constituents:

- Articles and references retrieved from data bases: PubMed, Toxline. Search terms: *Eleutherococcus, Acanthopanax, Syringin, Siberian Ginseng*
- Libraries: EMA library, University of Latvia, Rigas Stradinu University, The State Agency of Medicines of Latvia.
- Handbooks, textbooks and Pharmacopoeias

For the first 5-year revision of the monograph a literature research was carried out in the data bases Pubmed and Toxline with the following keywords: "*Eleutherococcus, Acanthopanax, Syringin, Siberian Ginseng*"; publication year 2006 to June 2013. In summary more than 200 publications were listed. In addition, literature was provided by Kooperation Phytopharmaka in response to the the call for scientific data for the systematic review of the monograph. The references were identified that could have a possible impact on the revision of the assessment report, monograph and list entry.

This assessment report is based on the summary of the most relevant scientific literature which includes more than 300 articles. Hundreds of other articles related to research work are summarised in various monographs and reviews (Aicher *et al.,* 2006, 2012; Barnes *et al.,* 2007, Bleakney, 2008; Blumenthal *et al.,* 1998; Brekhman, 1968a; Brekhman & Kirillov 1968b; Collisson, 1991; Dardymov, 1976a; Duke, 1985; Duke *et al.,* 2002; Farnsworth *et al.,* 1985; Gardner *et al.,* 2013; Halstead *et al.,* 1984; Huang *et al.,* 2011a; Mills *et al.,* 2005; Phillipson *et al.,* 1984; Sonnenborn *et al.,* 1993; WHO , 2002; ESCOP, 2009; Panossian, 2003; Panossian & Wagner,2005; Panossian *et al.,* 2013b, Wagner *et al.,* 1994, Wagner, 1995; Williams, 1993). These texts were also used in preparing this assessment report.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

References are going back at least until 1960 (Brekhman, 1960). There are pharmacological and clinical studies and reviews published in medical, pharmacological Journals, starting from 1957. In 1962 an Eleutherococcus root extract was approved by the former Soviet Union Pharmacological Committee for clinical use as a "stimulant". In 1966 Eleutherococcus root was recommended for use in the Soviet space program (Belay *et al.,* 1966). In 1968 Brekhman published the first book on the subject entitled "Eleutherococcus". After that, results of many tests which have been performed in Russia have been verified by researchers all over the world (Fulder, 1980).

In fact Eleutherococcus root has been used in medicine for many decades. Eleutherococcus root is in medicinal use in France (Pharm. Franc, 10), in Germany (Aicher *et al.,* 2006, 2012), in Russia (Ross Ph XI, Mashkowsky, 1997), in the United Kingdom (British Herbal Pharmacopoeia, 1999) and in China (Chen & Chen, 2004; Tang *et al.,* 1992).

Since the first article was published by Brekhman in 1960, over 1,000 articles have appeared. The following reviews of studies performed in the former Soviet Union are available: Grinewicz, 1966; Brekhman, 1968a; Dardymov, 1976a; Halstead *et al.,* 1984; Farnsworth *et al.,* 1985; Sokolov, 2000. European traditional uses are summarised in the following monographs, reviews and handbooks: Betti, 2002; Collisson, 1991; Duke *et al.,* 2002**;** Blumenthal *et al.,* 1998; Sonnenborn *et al.,* 1993; WHO, 2002; Mills *et al.,* 2005; Barnes *et al.,* 2007; Bleakney, 2008; ESCOP, 2009; Aicher *et al.,* 2006, 2012; Huang *et al.,* 2011a; Gardner *et al.,* 2013**;** Panossian *et al.,* 2013b; Wichtl, 2009; Willuhn, 2003; Alternative Medicine Review, 2006; Schilcher, 2008; Hänsel, 1980; Meyer, 2011; Panossian *et al.,* 2009a, Panossian & Wikman, 2009b.

Preparations from Eleutherococcus root, including powdered root, have been in medicinal use in Germany prior to January 1978 when corresponding medicinal products were notified to the German agency.

Eleutherococcus root is now widely offered in pharmacies, health food stores and as food supplements in the United States, Canada and in Europe, though not always as a product that conforms to pharmacopoeial requirements (Barna, 1985; Awang, 1996).

Eleutherococcus root is known in Chinese traditional medicine as “Ci-wu-jia” (Foster, 1996; Winston *et al.,* 2007); traditional of the Far East (Schroeter, 1975). Duke, 1985; reported that the plant was used in the North-eastern city of Harbin, China, as a folk remedy for bronchitis, heart ailments, and rheumatism. Referring to representatives from the China National Native Produce Corporation, Duke also reported that regular use of the plant is thought to help to restore vigour, improve general health, restore memory, promote good appetite and to increase longevity, basically serving as a preventive medicine and general tonic. Lin & Huang, 2000 has reported that Eleutherococcus is a popular folk medicine used in patients with hepatitis and cancer in Taiwan.

The following information about products currently on the market was obtained from the Member States following a new request in May 2013.

Germany

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1.	Eleutherococcus root dry extract (15-18:1); ethanol 36% (v/v)	On the market prior to 1978	soft capsule	2 x daily 1 soft capsule with 100 mg extract	As a tonic for invigoration in fatigue and impairment, in decreasing capability and power of concentration.
2.	Eleutherococcus root liquid extract (1:1); ethanol 34% (v/v)	On the market prior to 1978	oral liquid	3 x daily 5 ml liquid with 20 g fluid extract	As a tonic for invigoration in fatigue and impairment, in decreasing capability and power of concentration.
3.	Eleutherococcus root (17-25:1); ethanol 30% (v/v)	On the market prior to 1978	coated tablet	3 x daily 1 coated tablet with 42 mg extract	As a tonic for invigoration in fatigue and impairment, in decreasing capability and power of concentration.
4.	Eleutherococcus root powder	On the market prior to 1978	powder	3 x daily 1 g powder	As a tonic for invigoration in fatigue and impairment, in decreasing capability and power of concentration.
5.	Eleutherococcus root extract (1:11.3); sweet wine	On the market prior to 1978	oral liquid	3 x daily 10 ml (1/2 cup) oral liquid with 10 g extract 100 g (=97.5 ml) contains 100 g extract	As a tonic for invigoration in fatigue and impairment, in decreasing capability and power of concentration.
6.	Eleutherococcus root (15-18:1); ethanol 28% (v/v)	On the market prior to 1978	hard capsule	1 x daily 1 hard capsule with 140 mg extract	As a tonic for invigoration in fatigue and impairment, in decreasing capability and power of concentration.
7.	Eleutherococcus root dry extract (15-17:1); aqueous	On the market prior to 1978	lozenge	2 x daily 1-2 lozenge with 45 mg extract	As a tonic for invigoration in fatigue and impairment, in decreasing capability and power of concentration.
8.	Eleutherococcus root extract (1:20); sweet wine, aromatic with Absinthii herba	On the market prior to 1978	oral liquid	3-4 x daily 1 cup (20 ml) with 8.24 g extract 100 ml (=103g) contains 41.2 g extract. Finished product contains 0.049% Absinthii	Herbal medicinal product traditionally used to improve general condition. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-

				herba as flavouring	standing use.
9.	Eleutherococcus dry extract (16-24:1); ethanol 35% (v/v)	On the market prior to 1978	coated tablet	3 x daily 1 coated tablet with 10 mg dry extract	Herbal medicinal product traditionally used to improve general condition. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use.
10.	Eleutherococcus root liquid extract (1:1); ethanol 30% (v/v)	On the market prior to 1978	oral liquid	2 x daily 1 cup (5 ml) with 10 g fluid extract	Herbal medicinal product traditionally used to improve general condition. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use.

Contraindication: Arterial hypertension

Spain

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1.	Powdered herbal substance	Since October 2010	hard capsules	Oral use 1000-1800 mg per day.	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness. According to HMPC monograph.

Denmark

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1.	Powdered root	Since 1996	Capsules (250 mg/capsule)	2 capsules in the morning and 2 capsules in the middle of the day. Dosage may be increased to 3x2 capsules. Not to be taken for more than 3 months. Not to be used for children below 12 years.	Herbal medicinal product against tiredness and in periods of reconvalescence. (WEU)

Combination product: *Eleutherococcus senticosus* extractum root, 7.2 mg corresponding to 120 mg dry root, tablets (since 1997) – combination product with Andrographis paniculata herba. Posology - 4 tablets 3 times daily. Not to be used for more than 2-3 months. Not to be used for children below 12 years. Indications - herbal medicinal product for the relief of symptoms of cold. Herbal medicinal product against tiredness and in periods of reconvalescence

France

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1.	Powdered herbal substance	Since 1981	Hard capsules (250 mg/capsule)	1 to 2 capsules twice daily.	Traditionally used in functional asthenia

Lithuania

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1.	Liquid extract (1:1), ethanol 40% v/v.	Since 1998	Oral drops, solution (1 ml of oral drops contains 1 ml of liquid extract)	Adolescents over 12 years of age, adults, elderly 20 drops 2-3 times daily	Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness.

Sweden

No	Preparation	Period of medicinal use	Dosage form	Posology	Indication
1.	Dry extract (corresponding to 243.1-429 mg dry root), extraction solvent ethanol 70%; water	Since 1978, reclassifed to THMP 2009	Tablet (14.3 mg extract/tablet) The product also contains vitamins B1 (thiamine hydrochloride), B6 (pyridoxine hydrochloride), B12 (cyanocobalamin) and vitamin E (alpha-tocopherol acetate).	Adults, elderly and adoscelents over 12 years of age: 1 tablet 2-4 times daily	Traditional herbal medicinal product used as adaptogen in case of decreased performance such as fatigue and sensation of weakness. The indications are based solely on experience and use during a long period of time. Product information harmonised with current HMPC monograph

Assessor's overall conclusion on the traditional medicinal use

Based on the information found in literature and information provided by Member States, a period of at least 30 years of medical use as requested by Directive 2004/24EC for qualification as a traditional herbal medicinal product is documented for the preparations included in the monograph and in the list entry.

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

The following indications have been reported in literature for Eleutherococcus root:

- As a tonic in case of decreased performance such as fatigue and sensation of weakness, exhaustion, tiredness and loss of concentration (Brekhman, 1968a; Halstead *et al*., 1984; Duke, 1985; Aicher *et al*., 2006, 2012; Blumenthal *et al*., 1998; Mashkowsky, 1997, Szolomicki *et al*., 2000; ESCOP, 2009; Hartz *et al*., 2004);
- As a prophylactic and restorative tonic for enhancement of mental and physical position for functional asthenia, strengthening and normalizing, as well as convalescence (Zotova, 1966; Batin *et al*., 1981; Berdyshev, 1977; Farnsworth *et al*., 1985; Asano *et al*., 1986b; Turbina *et al*., 1986; Wagner *et al*., 1992; Obolentseva *et al*., 1988; Blumenthal *et al*., 1998; Goulet *et al*., 2005; ESCOP, 2009);
- As adaptogen, to increase body resistance to such stressful exposures as heat, cold, physical exhaustion, viruses, bacteria, chemicals, extreme working conditions, noise, pollution (Baburin, 1966a, 1966b; Berdyshev, 1977; Brekhman & Mayansky, 1965a; Brekhman, 1965b; 1966, 1968a, 1977, 1980, 1982b; Schezin *et al*., 1977, 1981; Demin, 1977; Gagarin, 1977; Galanova, 1977; Kalashnikov, 1977, 1986; Bulanov *et al*., 1981; Lindendbraten *et al*., 1981; Shornikov *et al.,* 1981a, 1981b; Wikman, 1981; Marochko *et al*., 1982; Sosnova *et al*., 1984; Sosnova, 1986; Shadrin *et al*., 1986; Collisson, 1991; Dowling *et al*., 1996; Azizov, 1997; Bucci, 2000; Glatthaar-Saalmüller *et al*., 2001; Arushanyan *et al*., 2003;).
- Eleutherococcus root was commonly used in Russia in oncology hospital departments to increase the tolerance of the patients to the adverse effects of chemotherapy and radiation therapy (Gvamichava *et al*., 1966; Kupin *et al*., 1986a, 1986b).

From the market overview the following indications and respective herbal preparations were identified:

In Germany:

- As a tonic for invigoration in fatigue and impairment, in decreasing capability and power of concentration: powdered herbal substance; dry extract (15-18:1, ethanol 36%(v/v)); liquid extract (1:1; ethanol 34%(v/v)); extract (17-25:1, ethanol 30% (v/v)); extract (1:11.3; sweet wine); (15-18:1; ethanol 28% (v/v)); dry aqueous extract (15-17:1).
- Herbal medicinal product traditionally used to improve general condition. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use: extract (1:20); sweet wine, aromatic with Absinthii herba; dry extract (16-24:1, ethanol 35% (v/v)); fluid extract (1:1; ethanol 30% (v/v)).

In Spain:

- Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness: powdered herbal substance.

In Denmark:

- Herbal medicinal product against tiredness and in periods of reconvalescence: powdered herbal substance.

In France:

- Traditionally used in functional asthenia: powdered herbal substance.

In Lithuania:

- Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness: liquid extract (1:1; ethanol 40% (v/v)).

In Sweden:

- Traditional herbal medicinal product used as adaptogen in case of decreased performance such as fatigue and sensation of weakness. The indications are based solely on experience and use during a long period of time: Dry extract (corresponding to 243.1-429 mg dry root), ethanol 70%, water).

For more detailed information please see section: Information about products on the market in the Member States.

Based on the available literature and the information provided by Member States on traditional use, the following indication is recommended:

Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness. The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.

The requirements of medicinal use in these indications for at least 30 years (including at least 15 years within the EU) according to Directive 2004/24/EC is considered fulfilled for the following preparations:

1) Comminuted herbal substance
2) Powdered herbal substance
3) Liquid extract (DER 1:1, extraction solvent ethanol 30-40% v/v)
4) Dry extract (DER 13-25 : 1, extraction solvent ethanol 28-40% v/v)
5) Dry extract (DER 17-30 : 1, extraction solvent ethanol 70%, v/v)
6) Dry aqueous extract (DER 15-17:1)
7) Tincture (ratio of herbal substance to extraction solvent 1:5, extraction solvent ethanol 40% v/v)
8) Liquid extract (DER 1:11), extraction solvent sweet wine
9) Liquid extract (DER 1:20), extraction solvent sweet wine

During the 5-year revision of the monograph a traditional use of liquid extract (DER 1:11, extraction solvent sweet wine) and liquid extract (DER 1:20, extraction solvent sweet wine) were identified and added to the monograph.

Liquid extract DER 1:20, extraction solvent: sweet wine aromatised with Absinthii herba contains Absinthii herba as flavouring to gain a bitter taste; therefore Absinthii herba is not mentioned in the preparation description in the monograph. 100 ml of sweet wine contains 49.4 mg Absinthii herba; the finished product contains 0.049% Absinthii herba (corresponding to 16 mg Absinthii herba at the maximum recommended daily dose of 33 g extract).

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

Overview of the dosage reported in literature:

The dosages used in studies to determine the prophylactic use of the Eleutherococcus root fluid extract ranged from as little as 0.5 ml every other day to as much as 22 ml per day. In experiments with healthy persons, stress-mitigating effects have been reported by giving single doses from 2.0 up to

16.0 ml of the extract (p.o.). The usual dose employed ranged from 0.5 to 6.0 ml, given one to three times a day for a period of up to 35 days. Additional courses of Eleutherococcus root extract therapy were sometimes employed up to a series of eight courses. At the end of each course there has been a rest period of two to three weeks, during this period no extract was administered.

It is reported that patients should start on a low dose, i.e. 500 mg of powdered root, or its equivalent, three times a day; if no effect has been noted after two weeks, the dose can be increased to 1 g (Collison, 1991).

Other posologies that were reported in literature are: 2-3 g per day of comminuted Eleutherococcus root for teas for up to three months, as well as aqueous alcoholic extracts for internal use. A repeated course is feasible. Internally: ethanol fluid extract of Eleutherococcus root is given 20 to 40 drops two to three times daily before meals (daily dose to 80 drops). The cure lasts 25 to 30 days; then it is repeated with one to two-week breaks two to three times. If necessary, cures can be carried out without interruption for several years. Infusion: 2-3 g in 150 ml of water; fluid extract (1:1)): 2-3 ml; tincture (drug to solvent ratio 1:5): 10-15 ml (Brekhman, 1968a).

German Commission E Monographs (Blumenthal et al., 1998; original monograph published in 1971)
Dosage: 2-3 g of root or equivalent preparations/daily
Duration of use: generally up to 3 months. A repeated course is feasible.

Herbal medicines. A guide for Health Care Professionals (Newall et al., 1966, Barnes et al., 2007)
Daily dosage: dry root 0.6-3.0 g daily up to one month
Duration of use: up to one month

British herbal compendium (Bradley, 1992)
Daily dose 2-3 g (as powdered drug, cut drug for tea infusions or aqueous-alcoholic extracts)

Handbook of Medicinal Herbs (Duke et al., 2002)
Dosage: 0.5-4 g of dried root, 0.5-48 ml of alcoholic extract per day
Duration of use: up to 60 days

WHO.
2002 - Daily dosage: 2-3 g powdered crude drug or equivalent preparations

The essential guide to herbal safety (Mills et al., 2005)
Daily dosage: 2-3 g of dried root and rhizome or by decoction; 2 to 8 ml of a 1:2 liquid extract or equivalent in tablet or capsule form
Duration of use: The recommended regime for healthy people as an adaptogen is a course of 6 weeks followed by a 2 week break. This regime can be repeated for as long as necessary. For the treatment of specific illnesses, continous use is preferable

ESCOP, 2009
Dosage: adults 1-2 ml of fluid extract (1:1, ethanol 40% v/v) 1-3 times daily or 65-195 mg of dry extract (14-25:1, ethanol 40% v/v) daily. Other preparations corresponding to 2-3 g of dried root daily For oral administration
Duration of use: if symptoms persist or worsen after one month, medical advice should be sought

Hagers Handbuch (Aicher et al., 2006)
Dosage: 2-3 g or root as comminuted drug for herbal tea or equivalent aqueous-alcoholic extracts daily Liquid extract (1:1, ethanol 40% v/v) – 20-40 drops 2-3 times (daily dose up to 80 drops)
Duration of use: 25-30 days. Cure is repeated with one to two-week breaks two to three times. If necessary, cures can be carried out without interruption for several years.

On the basis the literature and information provided by Member States the following posology is proposed for adolescents over 12 years of age, adults and elderly:

Daily dose

- Comminuted herbal substance: 0.5-4 g of the comminuted herbal substance in 150 ml of boiling water as herbal infusion. 150 ml should be divided in one to three doses taken during the day.
- Powdered herbal substance: 0.75-3 g
- Liquid extract: 2-3 ml
- Dry extracts (ethanol 28-70% v/v) corresponding to 0.5-4 g dried root
- Dry aqueous extract (15-17:1): 90-180 mg
- Tincture: 10-15 ml
- Liquid extract (DER 1:11), extraction solvent sweet wine: 30 ml (31 g), corresponds to 2.7 g dried root
- Liquid extract (DER 1:20), extraction solvent sweet wine: 25-33 g, corresponds to 1.2-1.7 g dried root.

The daily dose can be taken in one to three doses.

Duration of use

Some authors recommend that Eleutherococcus root should not to be taken for more than 2 months. For chronic conditions such as fatigue, preparations have been used for three months. Most authors recommend that, if a course is repeated, the next course should start after a 10-14 days break.

In a more recent study, the effect did not persist after 4 weeks of use (Cicero *et al.,* 2004).

Traditional herbal medicinal products can only be accepted if they can be used without medical advice or diagnosis. The symptoms, should they persist for more than 2 weeks, might be a signal for a serious disease that needs medical advice. The HMPC decided therefore to limit the duration of use to 2 month and to refer the patient to medical advice after 2 weeks in case of persistent symptoms.

3. Non-Clinical Data

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

Reference is made to the HMPC reflection paper on the adaptogenic concept (EMEA/HMPC/102655/2007).

Pharmacological studies in connection with the term “adaptogen”.

The concept of “adaptogens” is not well-known to Western medicine. When more than 50 years ago physicians of West Europe used this type of medicines terms such as a “roborants” (strengthening substances), “tonics” (which restore normal tone to tissue) and “alteratives” (which cause favourable changes in the processes of nutrition and repair) were used. In 1958 the term “resistogen” or “adaptogen” was introduced by Soviet scientists with the view to describe the actions of Eleutherococcus root.

The heterogenicity of pharmacological studies relates to the general concept that Eleutherococcus root is expected to increase unspecific resistance to various "stressors". Eleutherococcus root is often described as having a "stimulating and tonic effect" on the body. Stimulating action refers to the ability of medicinal substances to increase the work capacity of the organism after a single dose of the preparation. The tonic effect of a substance refers to the results obtained after prolonged doses of the medicament. This effect is reported to be manifested by an increase in work capacity, not only during the time period that the substance is being used, but for a sustained period of time thereafter (Dardymov, 1966, 1972a, 1982). Many pharmacological studies have been published on experiments that were designed to demonstrate the "adaptogenic" or "normalising" effects of Eleutherococcus root extracts (prepared with ethanol/water) in animals exposed to a variety of adverse conditions (stress, immobilisation, chemical challenge, etc.), and to elucidate the mechanism for these effects (Farnsworth *et al.,* 1985). In more recent research, adaptogens are defined as metabolic regulators which increase the ability of an organism to adapt to environmental stressors and prevent damage to the organism by such stressors (Panossian *et al.,* 1999b).

Pharmacological data regarding the herbal substance and herbal preparation

Pharmacological data from combinations

Panossian *et al.,* 2009a: Experiments were carried out with BALB/c mice taking ADAPT-232® forte, a fixed combination of extracts of *Eleutherococcus senticosus*, *Schisandra chinensis* and *Rhodiola rosea* (extract SHR-5), characterised for the content of active markers eleutherosides, schisandrins, salidroside, tyrosol and rosavin and in doses of about 30, 90 and 180 mg/kg for 7 consecutive days followed by forced swimming test to exhaustion. ADAPT-232® forte strongly augmented endurance of mice, increasing the time taken to exhaustion in a dose-dependent manner from 3.0+/-0.5 to 21.1+/-1.7 min, approximately seven fold. Serum Hsp72 was measured by EIA both in normal and stressful conditions before and after the swimming test. Repeated administration of the adaptogen dose - dependently increased the basal level of Hsp72 in the serum of mice from 0.8-1.5 to 5.5-6.3 pg/ml. This effect was even stronger than the effect of stress, including both physical (swimming) and emotional impacts: 3.2+/-1.2 pg/ml. The cumulative effect of stress and adaptogen was clearly observed in groups of animals treated with adaptogen after swimming to exhaustion, when serum Hsp72 increased to 15.1+/-1 pg/ml and remained at almost the same level during the 7 days. The authors concluded that adaptogens induce increase of serum Hsp72, regarded as a defence response to stress, and increase tolerance to stress (in the model combination of physical and emotional stresses). It can be suggested that increased tolerance to stress induced by adaptogen is associated with its stimulation of expression of Hsp70 and particularly with Hsp72 production and release into systemic circulation, which is known as a mediator of stress response involved in reparation of proteins during physical load.

Panossian *et al.,* 2012; found that adaptogens like the combination ADAPT-232® (a fixed combination of extracts from *Eleutherococcus*, *Schisandra* and *Rhodiola*) stimulate the expression of the neuropeptide Y in neuroglia cells.

Zhang *et al.,* 2012 showed that the combination of *Scutellaria baicalensis* and *Eleutheroccus senticosus* may be able to significantly block allergic early-and late-phase mediators and substantially suppresses the release of proinflammatory, and Th1-, Th2-, and Th17-derived cytokines.

Immunomodulating activity

The actions of Eleutherococcus root may be partially explained by its immuno-modulatory activities (Barenboim *et al.,* 1986; Barkan *et al.,* 1980; Kupin *et al.,* 1986a, 1986b; Bohn *et al.,* 1987, Sonnenborn *et al.,* 1993). The stimulating effect of Eleutherococcus root preparations is thought to involve the activation of T-lymphocytes by the eleutherosides. There may also be an indirect immunoenhancing effect mediated via the glycosides' more non-specific antistressor activity – as stress may decrease the activity of the immune system, particularly that of natural killer T-cells (Collisson, 1991). Eleutherococcus is an effective γ-interferon inducer, immunomodulator and anti-viral agent as reported by Zykov *et al.,* 1986; Kupin *et al.,* 1986b; Wacker & Eilmes, 1978; Wacker *et al.,* 1986; Wacker, 1983; Barenboim *et al.,* 1986.

In vitro

Eleutherococcus ethanolic extract have been shown to exhibit cytoprotective effects *in vitro* and antagonistic effects against different toxins in experimental animals (Brekhman Dardymov, 1969b; Anetai *et al.,* 1987; Monakhov, 1965; Sakharova *et al.,* 1985). Lymphocytes treated *in vitro* with lyophilised extract showed a wide spectrum of immunostimulating activity (activation of Tea, TEt and EAC-B-RFC and induction of γ-interferon production) both in cancer patients and healthy controls (Kupin *et al.,* 1986b).

An ethanolic fluid extract was shown to induce the production interleukin-1 and interleukin-6 but not interleukin-2 production. The effective concentration of the whole ethanolic extract ranged from 1.0-0.1 mg/ml for the enhancement of interleukin-1α production and 1.0-0.03 mg/ml for the enhancement of interleukin-6 production. It was concluded that the observed enhancing immunopharmacological activities on acute phase response mediators are the best exhibited by the induction with whole ethanolic extract whereas the species-specific and characteristic eleutherosides B and E are not associated with these acitivities. There was no indication that extract exerts a direct effect on the proliferation of T and B cells a part of the antigen-specific immunity where interleukin-2 is involved (Steinmann *et al.,* 2001).

A solution containing 0.98 g of an ethanolic extract of eleutherococcus per 5 ml increased phagocytosis of *Candida albicans* by human granulocytes and monocytes at concentrations between 0.0078 mg/ml and 3.14 mg/ml by 18%. In vitro transformation of granulocytes was not induced (Wildfeuer *et al.,* 1994).

An ethanolic extract derived from the roots of *Eleutherococcus senticosus* (0.98 g in 5ml solution) was found to influence markedly the cytokine synthesis of activated whole blood cultures of ten healthy volunteers. Whereas the synthesis of Rantes was increased over a wide range of concentrations, the release of IL-4, IL-5 and IL-12 was significantly inhibited. An inhibition at higher concentrations, switching to a stimulation at lower doses of the extract was seen with G-CSF, IL-6 and IL-13. From these particular immuno-pharmacological effects of *Eleutherococcus senticosus* authors suggested this herbal preparation possesses immuno-modulatory potency, rather than just being immuno-suppressive or –stimulating (Schmolz *et al.,* 2001).

Yi *et al.,* 2001; have investigated the effect of *Eleutherococcus senticosus* root on mast-cell-dependent anaphylaxis. There was demonstrated that *Eleutherococcus senticosus* root inhibited induced systemic anaphylactic shock at the dose of 1 g/kg by 50 p.c. When *Eleutherococcus senticosus* root was given as pre-treatment at concentrations ranging from 0.01 to 2.0 g/l, the histamine release from rat peritoneal mast cells induced was reduced in a dose-dependent manner. *Eleutherococcus senticosus* root (2 g/kg) also inhibited passive cutaneous anaphylaxis activated by anti-dinitrophenyl (DNP) IgE to 53.17+/-6.62 p.c. Conclusion that *Eleutherococcus senticosus* root may possess effective anti-anaphylactic activity (ESCOP, 2009).

Jeong *et al.,* 2001; investigated the effect of cell cultured Eleutherococcus (aqueous extract) by oral administration in mast cell-mediated allergic reactions. Eleutherococcus dose-dependently inhibited compound 48/80-induced systemic allergy with doses of 10(-2) to 1 g/kg 1 h before oral administration. Eleutherococcus inhibited systemic allergy with the dose of 1 g/kg by 25%. Eleutherococcus (1 g/kg) also inhibited passive cutaneous allergic reaction by 51%, dose-dependently inhibited histamine release from rat peritoneal mast cells. When Eleutherococcus (0.01 mg/ml) was added, the secretion of tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 in antidinitrophenyl (DNP) IgE antibody-stimulated mast cells was inhibited 39.5% and 23.3%, respectively. In addition, Eleutherococcus inhibited anti-DNP IgE antibody-stimulated TNF-alpha protein expression in mast cells. Authors conclude that Eleutherococcus may be beneficial in the treatment of various types of allergic diseases.

In vivo

Wikman, 1980; has reported experiments performed in 1963 and 1965 by Pichurina and Bronnikov who investigated the protective action of Eleutherococcus root towards infections and other harmful influences. In one experiment rabbits were contaminated with a cultivation of dysentery microbes (*Shigella flexneri*, 10^9 microbes per rabbit). One hour before the test, one group had been given 0.1 ml of Eleutherococcus root extract per 20 g of body weight. The control group remained untreated. Seventy-two hours later 36% of the animals in the control group were still alive whereas 74% of the animals in the Eleutherococcus root group survived.

Intraperitoneal administration of an ethanolic extract containing mainly eleutherosides B and D to mice at daily dose of 18 mg/animal for 1 week increased the cytostatic activity of natural killer cells by about 200%. It appeared that the eleutherosides stimulated macrophagal T-cell and possibly B cell mediated immunity (Barenboim *et al.,* 1986). Treatment of rats with an extract of Eleutherococcus for 14 days before γ-irradiation accelerated the restoration of blood nucleic acid levels to normal, delayed the nadir in blood leucocyte count for 1-3 days, and increased leucocyte count on days 10-30 after radiation compared to untreated, irradiated controls. The extract thus appeared to promote recovery from radiation effects rather than to protect against them.

Li *et al.,* 2013a; investigated effect of 10% *Eleutherococcus senticosus* aqueous extracts (root or fruit) on Drosophila gut immunity and concluded that eleutherococcus improved improved the survival rate, attenuated the death of intestinal epithelial cells, promoted the expression of antimicrobial peptide genes, and decreased the formation of melanotic masses, it has a protective effect on Drosophila gut immunity and stress response, and may contribute to the prevention of inflammatory diseases induced by pathogenic and toxic.

Antioxidant activity

In vitro

Chen *et al.,* 2008; investigated the antioxidant properties of 3 adaptogen extracts – *Rhodiola rosea, Eleutherococcus senticosus* (not specified extract) and *Emblica officinalis*. Extracts were investigated by screening their ability to scavenge singlet oxygen, hypochlorite and hydrogen peroxide by using chemilumiscent analysis. Furthermore, their ferric reduction /antioxidant power, iron chelating potential and protein thiol protective effect were also determined in order to determine whether these is also capable of preventing oxidative stress induced complications. Eleutheroccus showed the best potential for hypochlorite scavenging. It was concluded that antioxidant potential was proportional to the respective polyphenol content.

To determine whether heat environmental stress (HES) affects the livers of rats, it was investigated in microarray-based expression profiling using an Affymatrix Gene Chip Rat genome 230 2.0 Array. They

also examined the effects of *Eleutherococcus senticosus* aqueos extract (3 fold extraction) on the gene expression profile in rats subjected to heat environmental stress relative to rats that did not receive Eleutherococcus. HES induced changes in gene expression transcript profiles, including those related to fatty acid synthase activity, oxidoreductase activity and lipid peroxidation (LPO). Authors observed dramatically increased malondialdehyde (MDA) levels after HES, which indicates that HES caused LPO through the regulation of oxidative stress and LPO-related transcripts, as revealed by microarray. When Eleutherococcus was orally administered to the HES group, the number of candidate validation genes as well as the MDA content decreased in comparison to rats that did not receive Eleutherococcus. Furthermore, rats in the HES group that received orally administered Eleutherococcus experienced significantly lower oxidative stress, as indicated by the expression of certain genes. Based on the combined results of this study, authors concluded that Eleutherococcus acts as a strong antioxidant in addition to exerting anti-HES effects (Kim *et al.,* 2010).

Liang *et al.,* 2009; investigated the effect of *Eleutherococcus senticosus* saponins on the oxidative damage induced by hydrogen peroxide (H_2O_2) in cardiomyocytes. Treatment with Eleutherococcus saponins (600 mg/l) prior to H_2O_2 exposure increased cell viability, lessened the cardiomyocyte morphological change, and inhibited augmentation of lactate dehydrogenase activity in culture media and of the cellular malondialdehyde content. Furthermore, the activities of superoxide dismutase (89.55 +/- 6.93 U/mg), glutathione peroxidase (845.87 +/- 63.76 mU/mg), catalase (93.07 +/- 10.40 U/mg) and the content of reductive glutathione (8.91 +/- 1.06 µmol/mg) of cardiomyocytes were raised ($P < 0.05$). Taken together, the results of the study implicate that Eleutherococcus saponins protect cardiomyocytes against oxidative-stress injury through reduction of lipid peroxidation and enhancement of the activity of antioxidant defense.

In vivo

Antioxidant effects have been studied by Mikaelyan in intact rats by injecting mixture of Eleutheroccus glycosides. The authors concluded that Eleutherococcus suppresses the intensity of of the induced peroxide oxidation of lipids and lowers the level of background lipoperoxides in the blood, plasma, heart, liver and brain. Simultaneously, Eleutherococcus decreases the expenditure of the endogenic antioxidant vitamin E, increasing its content in the tissues, also suppresses the activity of the enzymes which remove and prevent the formation of lipoperoxides (Mikaelyan *et al.,* 1986).

Lin & Huang, 2000; studied the antioxidant activity of the Eleutherococcus crude extract and the hepatoprotective activities on CCl_4 or acetaminophen-induced toxicity in the rat liver. Results suggest that Eleutherococcus may exert some antioxidant effects.

Hong *et al.,* 2009; studied effects of an aqueos extract from cultured *Eleutherococcus senticosus* cells on the antioxidative defence system, oxidative stress and cell membrane fluidity in the liver Type 2 diabetes in the mouse as an animal which is genetically prone to develop insulin resistance and obesity/diabetes. The mice were orally administered extract (0.5 g/kg body weight) once a day for 12 weeks. The authors concluded that the extract strengthened the antioxidative defense system with an increased activity of antioxidant enzymes such as superoxide dismuthase, glutathione peroxidase and catalase, as well reduced the accumulation of reactive oxygen species such as superoxide radical and H_2O_2, which decrease the generation of oxidative damage substances, such as thiobarbituric acid reactive substances and lipofuscin, increase the membrane fluidity lowered by oxidative damage.

Wang *et al.,* 2010; evaluated different doses (75 mg/kg, 150 mg/kg and 300 mg/kg) of an aqueous extract of *Eleutherococcus senticosus* for the antioxidant activity against oxidative stress in mice induced by tert-butyl hydroperoxide (t-BHP) via histopathological observation of the liver, and detection of antioxidant enzyme activity, antioxidants concentration, and related gene and protein expression. *Eleutherococcus senticosus* aqueous extracts attenuated the morphological injury of liver induced by t-BHP and increased the activity of antioxidant enzymes and the ratio of reduced versus

oxidised glutathione (GSH/GSSG) in serum and liver homogenates. Medium and high doses of *Eleutherococcus senticosus* extract also elevated the gene expression of NF-E2-related factor-2 (Nrf2), but not superoxide dismutases (CuZnSOD, MnSOD), catalase (CAT), glutathione peroxidase (GPx) and Glutamate—cysteine ligase catalytic subunit (GCLC). Protein expression results showed that Nrf2 and the antioxidant enzymes were all increased significantly by medium and high doses of ASE. The results indicate that *Eleutherococcus senticosus* protects against oxidative stress, which may be generated via the induction of Nrf2 and related antioxidant enzymes.

Stress protective and anti-fatigue effects

Antistress properties and an antifatigue effect of the drug have been described by Kaznachejev, 1977; Kirillov, 1977; Baranov, 1982; Farnsworth *et al.,* 1985; Gvamichava *et al.,* 1966; Dalinger, 1966a.

There are studies that demonstrate that Eleutherococcus root extract counteracts the effect of different noxious substances or agents. Positive results have been described in application of Eleutherococcus root for reducing toxicity of biological toxins, physical factors, chemical compounds, including drugs, and ionising radiation as well as for its ability to increase human's resistance (Maianskii, 1962; Voskresensky, 1977; Voskresensky *et al.,* 1986; Yonezawa *et al.,* 1989; Collisson, 1991; Rukavishnikova, 2010).

It has been reported (Elkin, 1970) that Eleutherococcus root extract shortens the duration of the sleep induced in mice by hexobarbital, chloralhydrate, sodium barbital and ether. Brekhman, 1982b reported that Eleutherococcus extract raises the sensitivity threshold of test animals to narcotics (ether, chloralhydrate or sodium barbital) and to ethanol. A median lethal dose of 35% ethanol for mice was doubled as a result of single administration of Eleutherococcus root, while the prophylactic use of Eleutherococcus root for a period of 30 days caused a 2.5-fold increase of the DL_{50} value. These results point to show that Eleutherococcus root extract may enhance ethanol tolerance in test animals. In another experiment on rats (Brekhman, 1982b) confirmed this hypothesis.

It has been found that intraperitoneal injection of Eleutherococcus root in irradiated (X-ray) mice, at a dosage of 3.5 ml/kg for seven days, exerts a moderate radioprotective action (Collisson, 1991). Irradiated (X-ray) mice treated with ER extract are reported to survive five times longer than controls (Brekhman *et al.,* 1970b).

Kirillov & Dardymov 1966; has reported that Eleutherococcus root given daily to rats under various types of stress normalised the weights of the thyroid and adrenal glands (usually shrunken by stress) and eliminated any evidence of stress upon the functions of these glands. It has been proposed (Panossian *et al.,* 2007) that nitric oxide and cortisol may be used as appropriate stress markers that can be employed in the evaluation of the anti-stress effects of stress-protectors and adaptogens. In more recent studies it has been proposed that the beneficial stress-protective effect of adaptogens is related to the two levels of regulation: (1) in the level of the whole organism, where they support homeostasis and neuroendocrine regulation of the hypothalamic-pituitary-adrenal axis involving the stress hormones and other mediators of the stress response, such as cortisol, neuropeptide Y, nitric oxide, membrane bound G-protein receptors and molecular chaperones heat chock preoteins 70; (2) on the cellular level they modulate gene expression (transcriptional control of metabolic regulation) of key mediators of intracellular communications involved in stress–induced signal patways (Panossian *et al.,* 2009a, 2009b, 2012, 2013a, 2013b).

The total eleutherosides had no effect on oxygen utilisation by rat liver mitochondria with succinate, glutamate, or tetramethylphenyl substrates but did increase oxygen uptake in whole rat liver homogenates (Dardymov & Khasina, 1972d).

Glucocorticoids are major mediators of the stress response and directly suppress the natural killer (NK) activity. Thus, the response for body the stress is complex, involving metabolic, inflammatory, neuroendocrine, and immunological aspects. It has been speculated that the extracts of Eleutherococcus may have stress-reducing actions and consequently, may act on the reduction of NK activity and blood corticosterone elevations induced by stress (Fujikawa *et al.,* 2002).

In support of reports of the glucocorticoidlike effects *in vivo* for Eleutherococcus, an other study has shown that a 30% ethanol extract of Eleutherococcus roots bind to the estrogen receptor in rat uterus, mineralocorticoid, and glucocorticoid receptors in rat kidney *in vitro*, but not to the androgen receptor in rat kidney (Pearce *et al.,* 1982). Intraperitoneal administration of an aqueous extract of Eleutherococcus root to rats (3 mg/kg body weight) caused a significant increase in corticosterone levels 3 hours after injection, whereas adrenocorticotropic hormone levels remained unchanged (Winterhoff *et al.,* 1993a, 1993b). Nitrogen metabolism in normal and stressed rats has been reported to be normalised by s.c. 1 ml/kg Eleutherococcus extract (Feoktistova, 1966; Revina, 1966; Sal'nik, 1966). Anisimov *et al.,* 1972 tested the effect of compounds isolated from *Araliaceae* family plants on the biosynthesis of protein *in vitro.*

Kimura *et al.,* 2004; compared the effects of water extracts of *Eleutherococcus senticosus* bark on the swimming time, natural killer and blood corticosterone level using forced swimming stressed mice. It was concluded that eleutheroside E may contribute to the anti-fatigue action and to the inhibition of elevation of corticosterone induced by swimming stress. The working capacity of mice was assessed by forcing them to climb along an endless cord until complete exhaustion. *Eleutherococcus senticosus* root was administered one hour before the experiment. At a dose of 2.5 ml/kg the animals' running time was significantly increased to 72 minutes; controls could only endure 52 minutes, representing an increase of 38%. At a dose of 5 ml/kg the time increased to 76 minutes (45%). However, a further increase in dosage to 7.5 ml/kg did not further increase the animals' working capacity (Collisson, 1991).

Fujikawa *et al.,* 1996; have studied protective effects of aqueous or butanol extracts of Eleutherococcus from Hokkaido and its components on gastric ulcer in restrained cold water stressed rats. In the test with the extract prepared with hot water the result from a single oral administration (extract 50, 100 and 500 mg/kg per day dissolved in 1 ml distilled) water did not show any protective effect on gastric ulcer, but the protective effect was observed in a dose-dependent manner from the oral administration of the extract (50, 100 and 500 mg/kg per day) for 2 weeks. Pre-administration of the extract in a dose of 500 mg/kg showed the most potent inhibition without affecting either body or adrenal glands weights. Among various extracts from the stem bark, the n-butanol extract used for p. o. administration for 2 weeks showed an obvious inhibition of 61.1 p.c. on gastric ulcer, compared with the control group which was treated with distilled water in the same way. Chlorogenic acid and syringaresinol-di-O-β-D-glucoside, as the major components of the n-butanol extract, showed a significant inhibitory effect on gastric ulcer, at 21.4% and 51.3%, respectively.

It was investigated the effect of the hydroalcoholic extract of the stem bark of *Eleutherococcus senticosus* on the neuronal activation patterns of c-Fos expression in the rat brain. With Eleutherococcus administration, c-Fos accumulated in both the supraoptic nuclei (SON) and paraventricular nuclei (PVN), which regulate stress response. Only the caudal regions in the nucleus of the solitary tract (NTS), a locus innervating both the SON and PVN, were activated. Such a neuro-anatomical pattern associated with ASH suggests the possible involvement of these stress-related brain loci (Soya *et al.,* 2008).

Extracts of *Eleutherococcus senticosus* (contains 2.1% Eleutherosides B+E) and *Rhodiola rosea* increased the mean lifespan of the nematode *C. elegans* in a dose-dependent way. In at least four independent experiments, 250 microg/ml Eleutherococcus (SHE-3) and 10-25 microg/ml *Rhodiola*

(SHR-5) significantly increased life span between 10 and 20% (P < 0.001), increased the maximum lifespan with 2-3 days and postponed the moment when the first individuals in a population die, suggesting a modulation of the ageing process. With higher concentrations, less effect was observed, whereas at the highest concentrations tested (2500 microg/ml SHE-3 and 250 microg/ml SHR-5) a lifespan shortening effect was observed of 15-25% (P < 0.001). Both extracts were also able to increase stress resistance in *C. elegans*: against a relatively short heat shock (35°C during 3 h) as well as chronic heat treatment at 26°C. An increase against chronic oxidative stress conditions was observed in mev-1 mutants, and during exposure of the wild type nematode to paraquat (10 mM) or to lesser extent UV stress. Both adaptogens induce translocation of the DAF-16 transcription factor from the cytoplasm into the nucleus, suggesting a reprogramming of transcriptional activities favoring the synthesis of proteins involved in stress resistance (such as the chaperone HSP-16) and longevity (Wiegant *et al.,* 2009).

Huang *et al.,* 2011c; tried to ascertain the anti-fatigue property of *Eleutherococcus senticosus* by the load-weighted swimming test and the sleep deprivation test, as well as to isolate and characterise the active constituents. Animals (mice) were orally administered with the extract of *Eleutherococcus senticosus*. The anti-fatigue effects of four fractions (with different polarities from the 80% ethanol extract), different eluates (collected from D101 macroporous resin chromatography) and eleutheroside E, were examined based on the weight-loaded swimming capacity (physical fatigue) and the change of biochemical parameters in ICR mice. Moreover, the active fraction was later submitted to sleep-deprived mice (mental fatigue). The n-butanol fraction significantly extended the swimming time of mice to exhaustion. Furthermore, the 60% ethanol-water eluate, more purified eleutherosides (including eleutheroside E, E(2) and derivatives), were reported as active constituents. Two compounds were isolated, which were identified as eleutheroside E and E(2). The authors stated that eleutherosides possess potent abilities to alleviate fatigue both in physical and mental fatigue; in particular eleutheroside E. In another study, a liposoluble fraction of *Eleutherococcus senticosus* was administered orally to mice for 9 days. The swimming time to exhaustion was longer in the treatment groups (22.2-3.3, 25.5-4.8 min) than in the control group (13.7-1.2 min, $p < 0.05$). The plasma TG (triglyceride) and BUN (blood urea nitrogen) levels in the high dose (500 mg/kg) groups were decreased significantly compared with the control group. Plasma lactate dehydrogenase (LDH) was lower in the treatment groups than in the control group. Chemical analysis from GC/MS revealed that the main components of the liposoluble fraction of Eleutherococcus were saturated fatty acid (12.98%), unsaturated fatty acid (33.13%), unsaturated alcohol (27.46%) and diolefine (15.76%). In conclusion, the liposoluble fraction enhanced the forced swimming capacity of mice by decreasing muscle damage, effectively preventing the increase in blood urea nitrogen concentration and increasing fat utilisation. It is proposed that the antioxidant effect may be one of the antifatigue mechanisms of the liposoluble fraction of Eleutherococcus (Huang *et al.*, 2011b).

Zhang *et al.,* 2010; investigated the anti-fatigue activity in male Kunming mice of extracts of stem bark from *Eleutherococcus senticosus* using a forced swimming test. Mice were divided into four groups (three *Eleutherococcus senticosus* administered groups, 100, 200 and 400 mg/kg, and the control group). After four weeks, a forced swimming test was performed and the biochemical parameters related to fatigue were examined. The results suggested that *Eleutherococcus senticosus* could extend the swimming time to exhaustion of the mice, as well as increase the tissue glycogen contents, while decreasing the blood lactate and serum urea nitrogen contents. This indicated that *Eleutherococcus senticosus* has anti-fatigue activity and can elevate the exercise tolerance.

Rhim *et al.,* 2007; investigated the effects of *Eleutherococcus senticosus* on the time to exhaustion by treadmill exercise and on serotonin (5-HT) synthesis and tryptophan hydroxylase (TPH) expression in the dorsal raphe of rats by immunohistochemistry. *Eleutherococcus senticosus* increased the time to exhaustion by treadmill running and it suppressed the exercise-induced increase of 5-HT synthesis and

TPH expression. *Eleutherococcus senticosus* was effective as caffeine for increasing the exhaustion time in treadmill running and for reducing the exercise-induced increase of 5-HT synthesis and TPH expression in the dorsal raphe. The authors conclude that *Eleutherococcus senticosus* reduces fatigue during exercise by the inhibition of exercise-induced 5-HT synthesis and TPH expression in the dorsal raphe.

Shakhmatov *et al*., 2010; investigated changes in the hemostasis system of rats during extreme exercises. It has been observed that a single two-hour swimming exercise and an eight-hour imposed running in the treadbahn are accompanied by the expressed shifts in hypercoagulation with the signs of thrombinemia. On the background of the decrease in the anticoagulative and fibrinolytic activity it creates a serious threat of intravascular blood coagulation. The preliminary thirty-day course of Eleutherococcus extract (ethanolic extract, 1:1, dosage 0.25 ml/kg/day) eliminated the signs of intravascular blood coagulation.

Neuroprotective effects

In vitro

Tohda *et al*., 2008; investigated the effects of *Eleutherococcus* senticosus methanol and water extracts on the regeneration of neurites and the reconstruction of synapses in rat cultured cortical neurons damaged by amyloid beta Aβ-(25-35). Treatment with Aβ-(25-35) (10 microM) induced axonal and dendritic atrophies and synaptic loss in cortical neurons. Subsequent treatment with the methanol extract and the water extract of *Eleutherococcus senticosus* (10-1000 ng/ml) resulted in significant axonal and dendritic regenerations and reconstruction of neuronal synapses. Co-application of the extract and Aβ-(25-35) attenuated Aβ-(25-35)-induced neuronal death. Authors investigated neurite outgrowth activities of eleutherosides B and E and isoflaxidin, which are known as major compounds in *Eleutherococcus senticosus*. Although eleutheroside B protected against Aβ-(25-35)-induced dendritic and axonal atrophies, the activities of eleutheroside E and isofraxidin were less than that of eleutheroside B. Although the contents of these three compounds in the water extract were less than in the methanol extract, restoring activities against neuronal damages were not different between the two extracts. In conclusion, extracts of *Eleutherococcus senticosus* protect against neuritic atrophy and cell death under Aβ-(25-35) treatment, and one of active constituents may be eleutheroside B.

Bai *et al*., 2011; has published a similar study where a comprehensive evaluation of constituents was conducted to explore active components from *Eleutherococcus senticosus* which can protect against neuritic atrophy induced by amyloid β Aβ-(25-35) in cultured rat cortical neurons. The ethyl acetate, n-butanol and water fractions from the methanol extract of *Eleutherococcus senticosus* showed protective effects against Aβ-induced neuritic atrophy. Twelve compounds were isolated from the active fractions and identified. Among them, eleutheroside B, eleutheroside E and isofraxidin showed obvious protective effects against Aβ-induced atrophies of axons and dendrites at 1 and 10 μM.

Jin *et al.,* 2013; examined the mechanism of *Eleutherococcus senticosus* (ethylacetate fraction from aqueos extract of fruits) activity in antineuroinflammatory and neuroprotective processes. HO-1 is an inducible enzyme present in most cell lines. *Eleutherococcus senticosus* increased HO-1 expression, which reduced lipopolysaccharides (LPS)-induced nitric oxide/ROS production in BV2 cells. Moreover, the induction of HO-1 expression protected cells against glutamate-induced neuronal cell death. Activation of the p38-CREB pathway and translocation of Nrf2 are strongly involved in *Eleutherococcus senticosus* -induced HO-1 expression. Results showed that *Eleutherococcus senticosus* -induced HO-1 expression through the p38-CREB pathway plays an important role in the generation of anti-neuroinflammatory and neuroprotective responses. *Eleutherococcus senticosus* also increases the translocation of Nrf2 to regulate HO-1 expression. The authors concluded that *Eleutherococcus senticosus* serves as a potential therapeutic agent for neuronal disorders.

In vivo

The neuroprotective effects of a water extract of *Eleutherococcus senticosus* were investigated in transient middle cerebral artery occlusion (MCAo, 90 min occlusion, 24 h reperfusion) of Sprague-Dawley rats. The infarct volume was significantly reduced by 36.6% after the peritoneal injection of extract (100 mg [sol]kg) compared with the control. In the immunohistochemical study, the extract markedly inhibited both cyclooxygenase-2 and OX-42 expressions in the penumbral region at 24 h after MCAo. The authors suggest that *Eleutherococcus senticosus* has a neuroprotective effect by inhibiting inflammation and microglial activation in brain ischaemia (Bu *et al.,* 2005).

Bocharov *et al*., 2008; in his review article reports that phytoadaptogens (*Eleutherococcus senticosus* amoung them) take part in protecting brain neurons from various injuries. The ability of phytoadaptogens to have influence on neurodegenerative mechanisms at Parkinson's disease is discussed. The authors conclude that phytoadaptogens should be proposed for study or use as therapeutic modulators in neurodegenerative disorders including Parkinson's disease.

Chen *et al.,* 2011b; observed that Eleutherococcus saponins could enhance the viability of spinal motor neurons and have protective effects on hypoxic neurons.

Liu *et al.,* 2012b; studied the neuroprotective effect of an extract of *Eleutheroccus senticosus* against 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced mice model of Parkinson's disease and its mechanism was studied. The Parkinson's disease mice model was induced by MPTP-HCl, 30 mg/kg daily for 5 days. High dose group and low dose group were medicated with alcoholic (80% ethanol) extract of *Eleutheroccus senticosus* for 20 days. Doses amounted to 182 mg/kg and 45.5 mg/kg daily, respectively. The behavioral testing of mice was assessed using pole-climbing test. The levels of Dopamine (DA) and Homovanillic acid (HVA) in striatum were determined by Ultra-performance liquid chromatography combined with time-of-flight mass spectrometry (UPLC-ToF-MS). The levels of dopamine receptor 1 and 2 in striatum were assayed simultaneously with the help of an immunohistochemical method. The level of the Caspase-3 protein in the *substantia nigra* was analysed by Western Blot. From Day 5 during the administration of extract of Eleutheroccus senticosus, pole-climbing time in low and high dose group were significantly less than for the model group ($p<0.05$). Compared with the model group, the DA level of the striatum in low the dose group was significantly higher ($p<0.01$), the number of dopamine receptor 1 and dopamine receptor 2-positive cells in low and high dose groups were significantly less ($p<0.05$), the Caspase-3 protein level of the *substantia nigra* in low and high dose groups were significantly less ($p<0.05$). The authors concluded that the neuroprotective effect of the extract of *Eleutheroccus senticosus* may be able to protect C57BL/6 mice against MPTP-induced dopaminergic neuronal damage.

Li *et al.,* 2013; who had summarised herbal medicines with Anti-Parkinsonian activities, has included *Eleutherococcus senticosus* among compounds reported to be effective on Parkinson's disease experimental models *in vivo*.

Antiviral activity

In vitro

Eleutherococcus senticosus extracts are reported to inhibit the growth of a variety of viruses, bacteria and fungi. An ethanolic fluid extract inhibited the replication of human rhinovirus, respiratory syncytial virus and influenza A virus in cell cultures (Wacker & Eilmes, 1978; Wacker, 1983; Wacker *et al*., 1986).

The EC_{50} of the liquid extract was a 1/120 dilution in the case of rhinovirus and influenza A virus and 1/2240 in the case of respiratory syncytial virus. The effect of the fluid extract was affected neither by

heat stress nor by conversion to a dry extract preparation (Glatthaar-Saalmüller *et al*., 2001). According to Wildfeuer *et al*., 1994, the fluid extract of Eleutherococcus root increased the *in vitro* phagocytosis of *Candida albicans* by granulocytes and monocytes from healthy donors by 30-45%. The preparations did not induce *in vitro* transformation of lymphocytes and had no effect in either direction on intracellular killing of bacteria or yeasts (Glatthaar-Saalmuller *et al*., 2001).

When Eleutherococcus root liquid ethanolic extract (100 µg, after removal of ethanol) and a suspension of vesicular stomatitis virus were simultaneously introduced into mouse fibroblast culture, the growth of virus was not inhibited (Wacker & Eilmes, 1978). However, when the extract was introduced into the mouse fibroblast culture before contact with the virus, the cells became resistant to the virus. The duration of this effect, however, was only about 6 hours.

In vivo

Parenteral administration of a 33% ethanolic extract of the Eleutherococcus root for 15 days prior to induced infection (dose not specified) increased the resistance of mice and rabbits to listeriosis, an infection caused by *Listeria monocytogenes,* capable of producing meningitis in man and animals (Cherkashin, 1966, 1968). However, administration of the extract simultaneously with the bacteria increased the severity of the infection (Cherkashin, 1966).

The antiviral activity of an Eleutherococcus root ethanolic fluid extract was evaluated in experimental influenza infection. The virus and the extract were simultaneously administered intranasally to mice. The titre of influenza virus in the lungs of the animals was recorded over 6 days. On the 5^{th} and the 6^{th} day after infection marked virus titres were measured in the lungs of control animals, whereas no virus titre was found in the animals treated with Eleutherococcus root extract (Protasova *et al.,* 1986).

Anti-inflammatory activity

In vitro

Jung *et al*., 2007; investigated the inhibitory effects of *Eleutherococcus* senticosus on the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in LPS-activated macrophages. *Eleutherococcus* senticosus significantly attenuated LPS-induced iNOS expression but not COX-2 expression. In using the standard inhibitors mitogen-activated protein kinase (MAPKs) and protein kinase B (Akt), the results show that *Eleutherococcus* senticosus downregulates inflammatory iNOS expression by blocking c-Jun N-terminal kinases (JNK) and Akt activation.

The study by Yamazaki *et al*.,2007 was undertaken to analyse effects of 3 active compounds isolated from the stem bark of *Eleutherococcus senticosus*: (+)-Syringaresinol-di-O-beta-D-glucoside (SR), syringin, and isofraxidin on inflammatory functions in SW982 human synovial sarcoma cell system. When cells were exposed to SR, syringin, or isofraxidin, only isofraxidin had significant inhibitory effects on cell growth, although a slight inhibition was observed at the highest concentration of SR. SR suppressed the production of IL-6 at lower concentrations than syringin and isofraxidin. SR and syringin significantly suppressed the production of prostaglandin E(2), while isofraxidin suppressed only slightly. SR was more potent than syringin and isofraxidin at inhibiting the expression of IL-1beta, IL-6, cyclooxygenase (COX)-2 and matrix metalloproteinases (MMP)-1 mRNA, but was less potent than syringin at inhibiting the expression of MMP-2. It was further demonstrated that SR significantly reduced MMP-1 promoter luciferase activity and DNA-binding activity of transcriptional factors AP-1 and NF-kappaB. Taken together, these results suggest that SR, an active component of the stem bark of *Eleutherococcus senticosus*, modulates the inflammatory process involved in arthritis by suppressing various gene expression through inhibiting AP-1 and/or NF-kappaB activities.

Lin *et al*., 2008a; investigated the inhibitory effect of the stem bark dry aqueous extract of *Eleutherococcus senticosus* on the production of superoxide anion and hydrogen peroxide in mouse peritoneal macrophages *in vitro* and *in vivo*. Exposure of mouse peritoneal macrophages to *Eleutherococcus senticosus* extract significantly suppressed superoxide anion production induced by zymosan in a dose-dependent manner and significantly inhibited hydrogen peroxide production induced by phorbol 12-myristate 13-acetate (PMA) in a dose-dependent manner. Intraperitoneal administration of *Eleutherococcus senticosus* extract to KM mice reduced the ex vivo production of zymosan induced-superoxide anion and PMA-induced hydrogen peroxide by their peritoneal macrophages. Exposure to *Eleutherococcus senticosus* extract did not affect the cell viability or systemic toxicity. *Eleutherococcus senticosus* inhibited reactive oxygen species production by mouse peritoneal macrophages *in vitro* and in vivo and may be partly responsible for the anti-inflammatory function.

Lin *et al*., 2008b; examined the effects of *Eleutherococcus senticosus* dry aqueous extract on nitric oxide (NO) production and inducible iNOS gene expression in LPS plus interferon-gamma (IFN-gamma)-stimulated RAW264.7 macrophages and investigated its mechanisms of anti-inflammatory activity. RAW264.7 macrophages were treated with 10 microg/ml LPS plus 20U/ml IFN-gamma in the presence or absence of *Eleutherococcus senticosus* extract. NO production and iNOS gene expression were investigated. The effect of *Eleutherococcus senticosus* extract on oxidative stress-sensitive transcription nuclear factor-kappa B (NF-kappaB) activation was evaluated. *Eleutherococcus senticosus* extract significantly suppressed NO production and iNOS gene expression in a dose-dependent manner. ASE also reduced DNA-binding activity of NF-kappaB in LPS plus IFN-gamma stimulated RAW264.7 macrophages. Further studies indicated that LPS plus IFN-gamma-induced inhibitory factor-kappa B alpha (I-kappaBalpha) degradation and p65 nuclear translocation were inhibited in RAW264.7 macrophages exposed to ASE. Moreover, *Eleutherococcus senticosus* extract inhibited the LPS plus IFN-gamma mediated increase in intracellular peroxides production. These results suggest ASE suppresses iNOS gene expression through the inhibition of intracellular peroxides production, which has been implicated in the activation of NF-kappaB.

Soo *et al*., 2012; examined the anti-inflammatory activity of *Eleutherococcus senticosus* extract (ethylacetate fraction of aqueous extract) and its mechanism of action in *Porphyromonas gingivalis* LPS-stimulated macrophages. *Eleutherococcus senticosus* significantly induced the expression and activity of heme oxygenase-1 (HO-1), which is known to produce an anti-inflammatory effect, in RAW 264.7 cells, through NF-E2-related factor 2 (Nrf-2), Janus kinase, and extracellular signal-regulated kinase activation. *Eleutherococcus senticosus* also effectively suppressed the production of pro-inflammatory cytokines, tumor necrosis factor α, interleukin (IL)-1β, and IL-6, and decreased the nuclear translocation and transactivity of activator protein-1 (AP-1) and NF-κB by inhibiting the phosphorylation of IκB-α in Porphyromonas gingivalis LPS-stimulated macrophage cells. Furthermore, ASE inhibits signal transducer and activator of transcription (STAT)1 phosphorylation while it activates STAT3 phosphorylation in Porphyromonas gingivalis LPS-stimulated RAW 264.7 cells. Study suggests that *Eleutherococcus senticosus* produces anti-inflammatory effects on Porphyromonas gingivalis LPS-stimulated macrophages through a reduction in AP-1 and NF-κB activity, modulation of STAT1 and STAT3 phosphorylation, and upregulation of HO-1 expression through the activation of mitogen-activated protein kinase and Nrf-2 signaling pathways.

Eleutherococcus senticosus (dry ethanolic extract, standartised to Eleutheroside A 0.486%±0.046%) protected delayed neuronal death in the CA1 region of the hippocampus against global cerebral ischemia in rats with the recovery of spatial memory, which can be considered as the normal functioning of the hippocampus. It was concluded that regarding the immunohistochemical study, the effect of *Eleutherococcus senticosus* may be attributable to its anti-inflammatory properties through the inhibition of COX-2 expression, microglia and astrocyte expression (Lee *et al*., 2012).

Hepatoprotective effects

In vivo

Smalinskiene *et al*., 2009; investigated the effects of the *Eleutherococcus senticosus* liquid extract on the accumulation of Cd(2+) in liver and on the mitotic and apoptotic activity of liver cells after chronic intoxication by Cd(2+). Laboratory mice were given to drink solutions of different Cd2+ and ES concentrations for 8 weeks. Cd2+ concentration in mouse liver was detected using atomic absorption spectroscopy. Mitotic and apoptotic activity of liver cells was expressed as an estimated number of mitotic and apoptotic cells in randomly selected reference areas in a histological slide. *Eleutherococcus senticosus* combined with CdCl2 leads to a significant decrease of cadmium concentration in the blood and liver of experimental mice. *Eleutherococcus senticosus* decreased the cadmium-induced mitotic and apoptotic activity of liver cells.

Experimental studies were conducted on 4 groups of animals, each containing 20 rats: (1) intact animals (control); (2) the animals given inhaled nitric oxide at a concentration of 4.3 mg/m^3 for 6 min; (3) those were prophylactically administered amtizole (40 mg/kg 30 min before inhalation of nitric oxide with further 6-min inhalation; (4) those receiving Eleutherococcus for 3 weeks, followed by amtizole administration 30 min before nitric oxide inhalation and with further 6-min inhalation. After nitric oxide inhalation, animals' survival was 16%; the preadministration of amtizole enhanced the survival up to 50%; co-administration of Eleutherococcus and amtizole contributed to 80% survival. Inhalation of nitric oxides at a concentration of 4.3 mg/m^3 resulted in the impairment of hepatic xenobiotic detoxification system, the development of tissue hypoxia, fatty infiltration, and deterioration of hepatic etherifying function. Preadministration of the antihypoxant amtizole prior to inhalation favored less hepatic dysfunction. Preadministration of Eleutherococcus and further amtizole administration have a protective effect on hepatic antitoxic function and lipid metabolism (Kushnerova *et al*., 2008).

To evaluate the anti-steatosis action of *Eleutherococcus senticosus* stem bark, insulin-resistant ob/ob mice with fatty livers were treated with *Eleutherococcus senticosus* stem bark ethanol extract for an 8 week-period. *Eleutherococcus senticosus* stem bark ethanol extract reversed the hepatomegaly, as evident in reduction of % liver weight/body weight ratio. The extract also specifically lowered circulating glucose and lipids, and enhanced insulin action in the liver. These changes culminated in inhibition of triglyceride synthesis in non-adipose tissues including liver and skeletal muscle. Gene expression studies confirmed reductions in glucose 6-phosphatase and lipogenic enzymes in the liver. According to the authors, these results demonstrate that *Eleutherococcus senticosus* stem bark ethanol extract is an effective treatment for insulin resistance and hepatic steatosis in ob/ob mice by decreasing hepatic lipid synthesis (Park *et al*., 2006).

Antiproliferative effects

Influence of alpha-difluoromethylornithine (DFMO) and tincture of Eleutherococcus on radiation carcinogenesis and life span in rats has been studied. The results of the study demonstrate that DFMO as well as TSGR significantly improved survival and decreased incidence and multiplicity of malignant and benign tumors in rats subjected to ionising radiation. Beneficial effect on the rat survival rate and anticarcinogenic action of DFMO were more expressed compared with Eleutherococcus (Bespalov *et al*., 2012).

The use of an aqueous extract of Eleutherococcus in combination with either cytarabine or N6-(Δ2-isopentenyl) adenosine had additive antiproliferative effects on L 1210 leukemia cells *in vitro* (ESCOP, 2009).

Cardioprotective effects

A pretreatment with *Eleutherococcus senticosus* extract (1 ml/kg per os during 8 days) prevented the stress-induced damages of the rat heart. A chronic administration of *Eleutherococcus senticosus* extract increased the cardiac tolerance to the cardiotoxic action of D, L-isoproterenol and the arrhythmogenic action of epinephrine. The pretreatment with naloxone (2 mg/kg) completely eliminated both the cardioprotective action and the antiarrhythmic effect of the phytoadaptogen. A chronic administration of *Eleutherococcus senticosus* extract increased the beta-endorphin level in the rat blood plasma. It is suggested that the cardioprotective and antiarrhythmic effects of *Eleutherococcus senticosus* extract is also related to an increase in the endogenous opioid peptide levels. A chronic administration of *Eleutherococcus senticosus* extract had no effect on the arrhythmogenic effect of a 45-min coronary artery occlusion and did not change the necrosis/risk area ratio in rats (Maslov *et al*., 2007).

Chronic treatment by *Eleutherococcus senticosus* elevated the ventricular fibrillation threshold in rats with postinfarction cardiosclerosis (Maslov *et al*., 2009).

Antidepresant effects

Jin *et al*., 2013; studied the anti-depressant effects of *Eleutherococcus senticosus* extract (dry aqueous extract, standardised to 0.8% syringing and syringaresinol) using animal models of depression including the forced swimming and tail suspension tests. The anti-depressive mechanism of Eleutherococcus was explored by monitoring the levels of monoamine neurotransmitters including 5-hydroxytrylamine (5-HT), norepinephrine (NE), and dopamine (DA), as well as cAMP response element-binding (CREB) protein expression in the whole brain of mice following the tail suspension test. Results showed that intragastric administration of Eleutherococcus at a dose of 2000 mg/kg for seven days significantly reduced the duration of immobility in both the forced swimming test and the tail suspension test. According to the authors, these results indicate that Eleutherococcus possesses antidepressant-like properties. Pre-treatment with 2000 mg/kg of Eleutherococcus for seven days significantly elevated the levels of 5-HT, NE, and DA in the whole brain ofmice. Moreover, ASE at doses of 1000 and 2000 mg/kg significantly up-regulated the level of CREB protein. Taken together, the authors suggest that the anti-depressive mechanism of Eleutherococcus may be mediated via the central monoaminergic neurotransmitter system and CREB protein expression.

Glycose lowering effects

The eleutherosides are reported to potentiate the effect of insulin on glucose consumption *in vitro*, using the rat diaphragm (Dardymov & Khasina, 1972c).

It was investigated whether *Eleutherococcus senticosus* extract (dried aqueous extract) has a glucose absorption inhibitory action. The effects of Eleutherococcus on α-amylase and α-glucosidase activities, and on glucose uptake in Caco-2 cells was examined, as well as the effects of Eleutherococcus oral administration on glucose tolerance in type 2 diabetes mellitus model db/db mice. The addition of Eleutherococcus inhibited α-glucosidase activity but not α-amylase activity. The α-glucosidase inhibitory activity of Eleutherococcus was approximately 1/13 of that of acarbose. The addition of Eleutherococcus inhibited 2'-deoxy-D-glucose (DG) uptake in human intestinal Caco-2 cells, and the inhibitory activity of Eleutherococcus was approximately 1/40 of that of phloretin. Kinetic analysis of glucose uptake indicated that Eleutherococcus has no effects on DG uptake through passive diffusion, but that Eleutherococcus inhibits intracellular DG uptake chiefly by inhibiting transport via a glucose transporter. In the glucose tolerance study, db/db mice orally administered Eleutherococcus for 3 days showed significantly lower plasma glucose level than the control group 30 min after sucrose loading, without affecting plasma insulin levels. In addition, Eleutherococcus oral administration significantly

inhibited α-glucosidase activity in the small intestine mucosa extirpated from the mice (Watanabe *et al*., 2010).

Vasorelaxant

Kwan *et al*., 2004; investigated the vasorelaxant effect of the aqueous extract of the roots of *Eleutherococcus senticosus* using several *in vitro* vascular rings prepared from dog carotid artery, rat aorta and rat mesenteric artery. Eleutherococcus extract (0.04-0.8 mg/ml) caused concentration-dependent relaxation in dog carotid arterial rings. Similar endothelium-dependent vascular relaxant responses were also obtained with rat aortic and mesenteric arterial rings, except that it occurred over a relatively higher concentration range of Eleutherococcus (0.5-2.0 mg/ml). In conclusion, it was demonstrated that the vascular effect of Eleutherococcus is endothelium-dependent and mediated by NO and/or EDHF depending on the vessel size. Other vasorelaxation pathways, such as inhibition of K(+)-channels and activation of muscarinic receptors, may also be involved.

Pharmacological data regarding isolated constituents

Several studies on pharmacology of purified compounds from Eleutherococcus root have been carried out so far (Fang *et al.,* 1985; Wagner, 1985; Anisimov *et al.,* 1972; Yun-choi *et al.,* 1987; Shen *et al.,* 1991; Fu *et al.,* 2012; Chen *et al.*, 2011a; Song *et al.,* 2010; Gong *et al.,* 2013; Liu *et al.,* 2008; Niu *et al.,* 2007, 2008; Ahn *et al.,* 2013; Huang *et al.,* 2011a; Choi *et al.,* 2006; Yamazaki *et al.,* 2007, Yamazaki & Tokiwa,2010).

Anisimov *et al.,* 1972 have informed about the results of the investigation of the influence of triterpenes (eleutherosides I and M) and phenol glycosides (eleutherosides B, B_1 and E) of *Eleutherococcus senticosus* on the early embryogenesis of the sea urchin. It was shown that the eleutherosides I and M at concentrations of 0.5 and 1000 µg/ml respectively hinder cleavage of sea urchin eggs with a successive lysis of the blastomeres. Eleutherosides B, B_1 and E at concentrations ranging from 1 to 100 µg/ml do not influence cell division in the course of the first 6 hours of development.

<u>Eleutheroside B (Syringin)</u>

Anti-inflammatory effects

Song *et al*., 2010; investigated the therapeutic effect of syringin on adjuvant arthritis (AA) in rats and its mechanisms. The secondary inflammation of induced AA rats appeared on the 14th day; syringin and tripterygium glycosides (TG) were given by intragastric administration for 16 days from the 14th day. Treatment of AA rats with syringin and TG from the 22th day significantly attenuated the secondary hind paw swelling, as well as relieved the pain response and the polyarthritic symptoms of the whole body as compared with that of the AA model group. The suppressed lymphocyte proliferation and IL-2 production of splenic lymphocytes in AA rats were reversed by treatment with syringin. Meanwhile, syringin remarkably down-regulated IL-1 beta, TNF-alpha productions from peritoneal macrophage phi. These results indicate that anti-inflammatory effects of syringin on AA rats are mediated by modulating the immune function of abnormal cells and the balance of cytokines .

Hepatoprotective effects

Gong *et al*., 2013; investigated the effects and underlying mechanisms of syringin on LPS and D-galactosamine (D-GalN)-induced fulminant hepatic failure (FHF) in mice. Mice were administered syringin (10, 30 and 100 mg/kg-1, respectively) intraperitoneally (i.p) 30 min before LPS/D-GalN then mortality and liver injury were evaluated subsequently. Authors found that syringin dose-dependently

attenuated LPS/D-GalN-induced FHF, as indicated by reduced mortality, inhibited aminotransferase and malondialdehyde (MDA) content, an increased glutathione (GSH) concentration and alleviated pathological liver injury. In addition, syringin inhibited LPS/D-GalN-induced hepatic caspase-3 activation and hepatocellular apoptosis, myeloperoxidase (MPO) activity and intercellular adhesion molecule-1 (ICAM-1) expression, as well as hepatic tissues tumor necrosis factor-alpha (TNF-α) production and NF-κB activation in a dose-dependent manner. These experimental data indicate that syringin might alleviate the FHF induced by LPS/D-GalN through inhibiting NF-κB activation to reduce TNF-α production.

Hypoglycaemic activity

Plasma glucose decreased was observed in a dose-dependent manner 60 min after intravenous injection of syringin into fasting Wistar rats. In parallel to the decrease of plasma glucose, increases of plasma insulin level as well as the plasma C-peptide was also observed in rats receiving same treatment. The results suggest that syringin has an ability to raise the release of acetylcholine from nerve terminals, which in turn to stimulate muscarinic M3 receptors in pancreatic cells and augment the insulin release to result in plasma glucose lowering action (Liu *et al*., 2008).

Niu *et al*., 2007; employed streptozotocin-induced diabetic rats (STZ-diabetic rats) as type 1 diabetes-like animal models to investigate the mechanism(s) of antihyperglycemic action produced by syringin. The obtained results suggest that syringin can enhance the secretion of beta-endorphin from adrenal medulla to stimulate peripheral micro-opioid receptors resulting in a decrease of plasma glucose in diabetic rats lacking insulin.

Niu *et al*., 2008 showed the ability of syringin to enhance glucose utilization and lower plasma glucose level in rats suffering from insulin deficiency.

Eleutheroside E

Stress protective activity

Huang *et al*., 2011d investigated the effect of Eleutheroside E on cognitive performances and biochemical parameters of sleep-deprived mice. Animals were repeatedly treated with saline, 10 or 50 mg/kg EE and sleep-deprived for 72 h by the multiple platform method. Briefly, groups of 5-6 mice were placed in water tanks (45 × 34 × 17 cm), containing 12 platforms (3 cm in diameter) each, surrounded by water up to 1 cm beneath the surface or kept in their home cage. After sleep deprivation, mice showed significant behavioral impairment as evident by reduced latency entering into a dark chamber, locomotion and correctly rate in Y maze, and increased monoamines in hippocampus. However, repeated treatment with Eleutheroside E restored these behavioral and biochemical alterations in mice.

Hypoglycaemic activity

Ahn *et al*., 2013; investigated the effect of Eleutheroside E containing *Eleutherococcus senticosus* extracts, as well as Eleutheroside E on hyperglycemia and insulin resistance in db/db mice. Eleutheroside E increased the insulin-provoked glucose uptake in C2C12 myotubes. Moreover, Eleutheroside E improved TNF- α -induced suppression of glucose uptake in 3T3-L1 adipocytes. Five-week-old db/db mice were fed a diet consisting of extract or Eleutheroside E for 5 weeks. Both were effective in improving serum lipid profiles and significantly decreased blood glucose and serum insulin levels. Eleutherococcus and Eleutheroside E supplementation effectively attenuated HOMA-IR. Glucose tolerance and insulin tolerance tests showed that Eleutheroside E increased insulin sensitivity. Immunohistochemical staining indicated that Eleutherococcus and Eleutheroside E protected pancreatic alpha and beta cells from diabetic damage. In addition, Eleutherococcus and Eleutheroside E improved

hepatic glucose metabolism by upregulating glycolysis and downregulating gluconeogenesis in obese type 2 diabetic mice. These data suggest that Eleutheroside E mediates the hyperglycemic effects of Eleutherococcus by regulating insulin signaling and glucose utilisation.

Polysaccharides

Immunomodulating activity

Polysaccharides fractions with molecular weigths in the range of 25 000 to 500 000 isolated from the alkaline aqueous extract of *Eleutherococcus senticosus* were given intraperitoneally to mice at 10 mg/kg. According to granulocytes and carbon clearance tests showed significant immunostimulating activities (Wagner *et al*., 1984, 1985). The effects were attributed to polysaccharides contained in the Eleutherococcus drug. The crude polysaccharide mixture and the heteroxylan stimulated phagocytosis in *in vitro* and *in vivo* tests (Wagner *et al*., 1984; Fang *et al*., 1985). In addition, according to Wagner *et al*., 1985, two polysaccharides in the root have been shown to display immunopotentiating activity (in phagocytosis), and immunoadjuvant activity (in B lymphocytes). Intraperitoneal administration of a polysaccharide fraction isolated from an aqueous root extract (10 mg/kg body weight) had exposed an immunostimulant activity in mice, as demonstrated by the colloidal carbon clearance test (Wagner *et al*., 1984).

Using C57BL mice as a model, continued daily injections of 100 mg/kg of PES significantly increased the PFC counts when evaluated on the fifth day. The anti-BSA antibodies have increased from 0.8 ± 0.3 to 1.9 ±0.5 on the sixth day. Their difference was significant ($P<0.01$). On the seventh day, the phagocytic activities were greatly enhanced as indicated by the phagocytic ratio and the phagocytic index (Shen *et al.,* 1991)

In more recent studies (Chen *et al.,* 2011a) a water-soluble polysaccharide obtained from *Eleutherococcus senticosus* leaves, was fractionated by DEAE–Sepharose fast-flow column chromatography, and purified by Sephadex G-75 gel-permeation column chromatography. The results showed that obtained polysacharides exhibited significantly higher immunomodulatory activities against the lymphocyte proliferation *in vitro*, pronounced reductive power, strong hydroxyl radical scavenging activity, moderate superoxide radicals and DPPH radicals scavenging activities.

Hypoglycaemic activity

Polysaccharide (ASP) from the roots of *Eleutherococcus senticosus* was evaluated as an adjuvant with metformin for antidiabetic therapy in alloxan-induced diabetic rats. The result showed that Eleutherococcus plus metformin had a more beneficial promotion for relieving the symptoms of diabetes and reversing liver and kidney damage to normal level than only metfomin administration to diabetic rats (Fu *et al*., 2012).

Isofraxidin

Antiproliferative effect

Isofraxidin (7-Hydroxy-6,8-dimethoxy-2H-1-benzopyran-2-one) in its anti-tumor effects on human hepatoma cell lines HuH-7 and HepG2 was investigated. Isofraxidin significantly inhibited hepatoma cell invasion, without affecting cell attachment or growth. Expression of 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced matrix metalloproteinase-7 (MMP-7) in hepatoma cells was inhibited by isofraxidin at the both mRNA and protein levels. This inhibition tended to be greater in cells inoculated at low density than in those at high density. Isofraxidin showed an inhibitory effect on the phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) in hepatoma cells, whereas

activator protein-1 (AP-1) DNA binding activity, nuclear factor-kappa B (NF-κB) nuclear translocation, and inhibitory kappa B (IκB) degradation were affected very little. These results indicate that isofraxidin inhibits expression of MMP-7 and *in vitro* cell invasion at a non-toxic level through inhibiting ERK1/2 phosphorylation in hepatoma cell lines. The authors suggest isofraxidin might become an effective agent for suppressing hepatoma cell invasion (Yamazaki & Tokiwa, 2010).

Saponins

Antioxidant, cardioprotective activity

Liang *et al*., 2010; investigated the effect of Acanthopanax senticosides B (a monomer of Eleutherococcus saponins) on oxidative damage induced by hydrogen peroxide (H_2O_2) of cardiomyocytes. Results demonstrated that Acanthopanax senticosides B (400 microg/ml and 200 microg/ml) can protect cells against oxidative injury of H_2O_2 (100 microM). Furthermore, the activities of superoxide dismutase (SOD), glutathione peroxidase, catalase and the content of reduced glutathione (GSH) of cardiomyocytes were also raised by Acanthopanax senticosides B. Taken together, the study implicated that Acanthopanax senticosides B protects cardiomyocytes against oxidative-stress injury induced by H_2O_2 through reduction of lipid peroxidation and enhances the activity of antioxidant defense.

Glycoproteins

Hepatoprotective effects

Choi, *et al*., 2006; studied the protective effect of a 30 kDa glycoprotein (GF-AS) isolated from the stem bark of *Eleutherococcus senticosus* against acute and chronic alcohol-induced hepatotoxicity. N-terminal amino acid sequence of GF-AS showed NH(2)-Val-Ala-Tyr-Pro-Trp-Ala-Gly-Phe-Ala-Leu-Ser-Leu-Glx-Pro-Pro-Ala-Gly-Tyr-. GF-AS significantly increases the activities of alcohol-metabolising enzymes, including alcohol dehydrogenase, microsomal ethanol metabolising system, and acetaldehyde dehydrogenase in rats acutely treated with alcohol, resulting in decreased plasma alcohol levels. GF-AS also increases the activities of antioxidant enzymes and glutathione level. Markers of liver injury induced by alcohol: elevated serum levels of aspartate aminotransferase, alanine aminotransferase, triglyceride and cholesterol, are reduced by GF-AS in both acutely and chronically treated rats. The activities of lipogenic enzymes including malic enzyme, glucose-6-phosphate dehydrogenase, and 6-phosphoglucuronic acid dehydrogenase in chronic alcohol-treated rats are significantly decreased by GF-AS. Furthemore, GF-AS improves histological change in fatty liver and hepatic lesions induced by alcohol. Collectively, GF-AS may alleviate alcohol-induced hepatotoxicity through increasing ethanol and lipid metabolism, as well as antioxidant defense systems in livers injured by acute- and chronic-alcohol treatment.

Pharmacodynamic interactions

Takahashi *et al.,* 2010; investigated the effect of *Eleutherococus senticosus* aqueous extract on intestinal drug transporter (P-glycoprotein, or P-gp) and peptide transporter activities in Caco-2 cells. The apical-to-basolateral (A-to-B) transport of digoxin, a P-gp substrate, was significantly increased by the addition of Eleutherococcus extract in a concentration-dependent manner. In contrast, the A-to-B transport of cephalexin, a peptide transporter substrate, was significantly decreased by the addition of Eleutherococcus extract in the same manner. The effects of Eleutherococcus extract addition on the kinetics of the uptake of rhodamine 123, a P-gp substrate, and Gly-Sar, a peptide transporter substrate, were also investigated. V (max) for rhodamine 123 uptake was significantly increased by Eleutherococcus extract addition compared with the control, whereas that for Gly-Sar

uptake was significantly decreased. On the other hand, K (m) and K (d) for rhodamine 123 and Gly-Sar uptake were not affected. Further investigations were conducted to clarify the effect of Eleutherococcus extract addition on P-gp activity. When Eleutherococcus extract was added to the apical side, B-to-A transport of rhodamine 123 was significantly decreased compared with the control. Furthermore, the amount of intracellular rhodamine 123 was increased by Eleutherococcus extract addition compared with the control. These results suggest that P-gp and peptide transporter activities are suppressed by Eleutherococcus extract addition in a non-competitive manner.

Nagai *et al.,* 2009; investigated *in vitro* the effects of 18 herbal extracts (Eleutherococcus extract among them) on SULT1A3 (phase II detoxifying enzyme of xenobiotics predominantly expressed in the intestinal epithelium) activity and the possibility of interaction between medicinal drugs and herbal extracts. The authors examined the inhibitory potencies of herbal extracts (in concentrations 10, 100, 1000 µg/ml) on the sulfation of dopamine, a typical substrate of SULT1A3, and ritodrine, a b 2 stimulant, by human recombinant SULT1A3. It was concluded that eleutherococcus extract did not inhibit SULT1A3 activity and thus should not increase the bioavailability of drugs for which the function of SULT1A3 at the intestinal epithelium is bioavailability-limiting. The IC50 values of Eleutherococcus (>1000 µg/ml) were exceedingly higher than the putative gastrointestinal concentration.

Data about a combination

Hovhannisiyan *et al.,* 2006 found that the concomitant application of Kan Jang (a standardised fixed combination of extracts from Andrographis paniculata and *Eleutherococcus senticosus*) and warfarin in rats did not produce significant effects on the pharmacokinetics of warfarin, and practically no effect on its pharmacodynamics.

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

The absorbtion and elimination of 3H-labelled eleutheroside B in rats after intraperitoneal administration was studied. The highest concentration of eleutheroside in the blood was observed after 15 minutes, then it dropped sharply in the period from 30 minutes to 4 hours after administration. Amounts of radioactivity in the urine and faeces indicated that elimination of eleutheroside B or its metabolites takes place mainly in the urine (90% within 48 hours, compared to not more than 3% in faeces (ESCOP, 2009).

In a subsequent study investigated the distribution of 3H-labelled eleutheroside B in major organs after intraperitoneal administration to rats. The liver and kidneys showed maximum incorporation within 75 minutes. High levels of labelled eleutheroside B were also found in the pancreas and medium levels in the hyphophysis, adrenals and spleen. Whereas elimination from the spleen was rapid, a more complex relationship was observed in the hypophysis and adrenals. In the hypophysis, the level of radioactivity after 30 minutes feel by 50% within 2 hours but then increased, reaching the initial level again within 4 hours. Adrenal glands also showed a tendency towards accumulation between 2 and 4 hours (ESCOP, 2009).

Ma *et al*., 2013; performed the pharmacokinetic study of Eleutheroside B and Eleutheroside E after oral administration at single dose of the single substances and an aqueous extract of *Eleutherococcus senticosus* as well as intravenous injection the single substances in healthy rats. A fast absorption process was found after oral administration of an aqueous extract from *Eleutherococcus senticosus* and single substances, respectively. The mean values of Tmax were 0.45 ± 0.112 h for single substances and 0.583 ± 0.144 h for an aqueous extract, respectively. The elimination half-life of Eleutheroside B and Eleutheroside E was less than 2.5 h for both. Oral absolute bioavailability of Eleutheroside B and Eleutheroside E was 3.30 ± 0.63% and 3.82 ± 0.86%, respectively, after oral and intravenous

administration at a single of Eleutheroside B and Eleutheroside E. Pharmacokinetic parameters revealed differences in the plasma between oral administration of an aqueous extract from *Eleutherococcus senticosus* and single substances. The AUC_{0-t} of Eleutheroside B after oral administration of an aqueous extract of *Eleutherococcus senticosus* was found significantly elevated (P = 0.034) compared with oral administration of single substances. In additional, AUC_0-t and $AUC_{0-\infty}$ of Eleutheroside E were significantly increased (P = 0.009 for AUC_{0-t} and P = 0.011 for $AUC_{0-\infty}$) by oral administration of an aqueous extract of *Eleutherococcus senticosus*, compared with oral administration of single substances. No significant difference was observed in C_{max} of Eleutheroside B and Eleutheroside E in rat plasma for an aqueous extract of *Eleutherococcus senticosus* and single substances. Moreover, enterohepatic circulation was found in Eleutheroside E after oral administration an aqueous extract of *Eleutherococcus senticosus* (Ma *et al*., 2013).

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

The toxicity of Eleutherococcus extracts is reported to be extremely low (Brekhman & Dardymov 1969b; Curtze, 1980; Vogt, 1981; Halstead *et al.,* 1984; Farnsworth *et al.,* 1985; Baldwin *et al.,* 1986; Hirosue *et al.,* 1986; Sonnenborn *et al.,* 1993, Gardner *et al.,* 2013). In clinical investigations of more than 20,000 patients and test persons no signs of acute toxicity have been observed (Fulder, 1980).

Single-Dose toxicity

The oral acute LD_{50} of powdered Eleutherococcus in mice is reported to be in the range of about 30 g/kg (Brekhman, 1968a; Farnsworth *et al.,* 1985). The oral LD_{50} value of the 33% ethanolic extract was about 14.5 g/kg body weight in mice (Brekhman, 1961, 1968a; Farnsworth *et al.,* 1985). Toxic effects at very high dosages (sedation, ataxia, tremor, or vomiting) are thought to be more readily due to the alcohol content of the extract than to a toxic effect of the Eleutherococcus compounds themselves (Curtze, 1980). Medon *et al.,* 1981 reported that a single dose of 3 g freeze-dried root extract did not cause death in mice.

Repeat-Dose toxicity

Eleutherococcus extract prepared by repeated extraction at 80°C with either ethanol or water were administered to rats at up to 400 mg/kg body weigth per day for 33-47 days. There were no appreciable differences in comparison with controls (Hirosue *et al.,* 1986).

After treatment of rats with an aqueous extract from Eleutherococcus (containing 0.6% of eleutheroside B and 1% of eleutheroside E) orally at 100 mg/kg and 500 mg/kg body weight or intraperitoneally at 3 mg/kg daily for 5 weeks no changes were observed in body weight or organ weigths (Winterhoff *et al.,* 1993a).

No toxic effects were observed in rats received 10 mg/kg daily of an ethanolic extract of Eleutherococcus for 2 months (Dardymov *et al.,* 1972 d, Davydov & Krikorian, 2000).

Rats administered 5 ml/kg daily of ethanolic extract of Eleutherococcus for 320 days showed no adverse reactions (Gardner *et al.,* 2013).

Preparations of the Eleutherococcus are reported to be non-toxic when administered over a long period of time. In clinical investigations of more than 6,000 patients and test persons no signs for toxicity have been observed. Eleutherococcus root is reported to be free from a cumulative toxicity (Steinmann *et al.,* 2001). In 29 patients that have been taken fluid extract of Eleutherococcus root for more than 5 years there no signs of toxic effects have been reported (Wikman, 1986).

Genotoxicity

In *in vitro* experiments, using the AMES assay with *Salmonella typhimurium* strains TA 100 and TA 98 and in the micronucleus test in mice, no mutagenic potential of Eleutherococcus root aqueous and ethanolic extracts has been found. An ethanolic extract up to 1 g/kg body weight and an aqueous extract at up to 1 g/kg were used (Hirosue *et al.,* 1986).

A "desmutagenic effect" has been observed in *Drosophila* (Sakharova *et al.,* 1985, 1986).

Carcinogenicity

Studies of carcinogenicity that would allow a reliable assessment have not been performed. In rats no carcinogenic potential of Eleutherococcus root was detected (Hirosue *et al.,* 1986). Anticancer effects were noted in experimental animals with transplanted tumours (Monakhov, 1965, 1967, Sakharova, *et al.,* 1985, 1986; Stukov, 1965, 1966, 1967).

Reproductive and Developmental Toxicity

No teratogenic or other effects have been observed in studies on pregnant animals (Brekhman *et al.,* 1982a; Brekhman, 1982b). Dardymov *et al.,* 1972d reported the absence of teratogenic effects in offspring from male and female Wistar rats given 10 mg/kg of total eleutherosides from Eleutherococcus root daily for 16 days.

Gordeichuk *et al.,* 1986, 1993 have studied preventive administration of Eleutherococcus root extract during prenatal and pre-embryonic periods of development. The extract prevented embryotoxic effect of subsequent treatment of pregnant rats with ethanol and sodium salicylate. Eleutherococcus root abolished embryotoxic and teratogenic effects of ethanol manifested against the background of experimental syndrome of iron deficit in pregnant females. Mechanism of its antiteratogenic action is supposed to be based on stimulation of cell detoxification mechanisms. Eleutherococcus root decreased embryotoxicant activity (P=0.01) and completely eliminated different teratogenes in rats (Chebotar, *et al.,* 1981).

Curtze, 1980 reported that teratogenicity studies on rats (13.5 ml of the fluid extract per kilogram body weight during the sixth to fifteenth day of pregnancy) did not reveal any negative effects on dams or foetuses.

Local Tolerance

Not applicable.

3.4. Overall conclusions on non-clinical data

Numerous studies on extracts and isolated constituents of Eleutherococcus root have been conducted *in vitro* and in animal models. Immunomodulating, antioxidant, stress protective, anti-fatigue, antiviral activity along with neuroprotective, hepatoprotective, cardioprotective, antiproliferative, antidepressant, glucose lowering effects have been detected. Results from studies performed with isolated constituents do not deliver a clear indication with respect to substances that may be responsible for the clinical effects. Eleutheroside B (syringin) and Eleutheroside E as main compounds might be responsible for stress protective, anti-inflammatory, hypoglycaemic and hepatoprotective effects, while polysaccharides are shown to have immunomodulating activity. However, the pharmacology of Eleutherococcus reflects the synergistic effects of its combined phytochemical constituents, especially those effects produced by the glycosides (eleutherosides) which are present.

The results of pharmacological investigations of Eleutherococcus have been summarised by Dardymov & Khasina, 1993. The authors postulate multiple effects on the human body, which involve:

- energy-mobilising impact, primarily through intensified utilisation of glucose;
- stress-protective effect conditioned by change in regulating the central nervous system and hormonal regulation;
- the action on the effects of hormones and their mediators, including changes in the contents of cyclic nucleotides and prostaglandins.

Limited data on pharmacokinetics are available on isolated compound Eleutheroside B after intraperitoneal injection; on Eleutherosides B and E after oral administration, as well on aqueous extract after oral administration and intravenous injection. Available *in vitro* study on interactions indicates some inhibitory effects by Eleutherococcus on activity of intestinal drug transporter (P-glycoprotein), however clinical relevance of this finding is not clear and no final conclusions can be drawn at the moment.

Data from toxicity studies (single-dose and repeat dose toxicity) are available for powdered drug, for ethanolic and aqueous extraxts. No toxic effects have been observed. Available data on reproductive and development toxicity studies in animals did not reveal any evidence of increased foetal damage. Eleutherococcus root aqueous and ethanolic extracts in AMES assay test with *Salmonella typhimurium* strains TA 100 and TA 98 and in the micronucleus test in mice showed a negative outcome. Although there is one of the strains of *Salmonella typhimurium* lacking in the published AMES test, the negative outcome in in-vivo micronucleus test can be regarded as sufficient for the development of a list entry for Eleutherococcus root aqueous and ethanolic extracts.

In conclusion, results from pharmacological studies support the medicinal use of Eleutherococcus as adaptogen and make plausible the use for symptoms of asthenia such as fatigue and weakness.The oral administration of Eleutherococcus root preparations can be regarded as safe under the conditions of use that are described in the monograph/list entry. Preparations of of Eleutherococcus root have been used in humans for many decades without any indication of serious risks.

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

Resistance to stress, adaptogenic potential

The main activity that is expected from an adaptogen is to enable an organism to adapt to and cope with unfavourable conditions, such as physical and psychological stress, infections, environmental pollutants, radiation and extreme climatic conditions. Numerous pharmacological studies, designed to measure the adaptogenic effects of Eleutherococcus root, have been performed in Soviet Union during the 1960s and 1970s (reviewed in Farnsworth *et al.,* 1985: Afanasiev *et al.,* 1973; Baburin, 1966a, 1966b, Baburin *et al.,* 1970a, Baburin & Polonsky, 1970b, 1972; Belonosov *et al.,* 1966, Berdyshev, 1970, 1977; Blokhin, 1966; Brandis & Pilovitskava*.,* 1966a, 1966b; Dalinger, 1966a, 1966b; Egorov & Baburin, 1966; Gagarin, 1977; Golikov, 1966a, 1966b; Novozhilov & Sil'chenko *,* 1985, Oleynichenko, 1966). For more information see section 4.2.2.

Facchinetti *et al.,* 2002; performed a study where 45 healhty volunteers (males and females) were subjected to the Stroop colour-word test as a stressful cognitive task before and after oral treatment

with Eleutherococcus (preparation and dosage not stated) or placebo for 30 days in a randomised, double blind design. Stress reactivity was measured as increases in systolic and diastolic blood pressure as well as in heart rate. Measurements were performed before, during and after testing. In both genders heart rate response to the stress test decreased after Eleutherococcus treatment, but not after placebo. In females systolic blood pressure also decreased in the Eleutherococcus group and remained unchanged after placebo. Authors concluded that the study demonstrated that treatment with *Eleutheroccus senticosus* is able to reduce cardiovascular responses to stress in healthy young volunteers while placebo was ineffective (ESCOP, 2009).

In a more recent study Lee *et al.,* 2008 examined the effects of *Eleutherococcus senticosus* supplementation on serum lipid profiles, biomarkers of oxidative stress, and lymphocyte DNA damage in postmenopausal women. Forty postmenopausal women, ages 40-65, were randomly divided into two groups: (1) control group (calcium) and (2) treatment group (500 mg calcium plus 500 mg *Eleutherococcus senticosus* extract daily (Eleutherococcus leaves, no further details known). Both groups were treated for 6 months. Blood samples were obtained before and after supplementation at 6 months. The following blood parameters were measured: serum total cholesterol, triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), serum malondialdehyde (MDA), ccdd protein-carbonyl (PC) levels, the degree of lymphocyte DNA damage by comet assay, total ferric reducing antioxidant power (FRAP), uric acid, and total bilirubin in serum. The treatment group had significant decreases ($p<0.001$) in serum LDL (127.54+/-29.79 mg/dL vs 110.33+/-22.26 mg/dL) and the LDL/HDL ratio (2.40+/-0.65 vs 2.11+/-0.58) after A. senticosus supplementation. Serum MDA concentrations decreased by 2.2% in the control group and by 12.61% in the treatment group after 6 months of intervention; however, the reductions were not significant in either group. Protein-carbonyl levels and lymphocyte DNA damage decreased significantly ($p<0.001$ and $p<0.05$, respectively) after 6 months of *Eleutherococcus senticosus* supplementation. The authors suggest that *Eleutherococcus senticosus* supplementation may have beneficial effects against oxidative stress and improve serum lipid profiles without subsequent side effects**.**

Shakhmatov *et al*., 2011; performed a study with Eleutherococcus liquid ethanolic extract in healthy young persons with different degrees of physical training. During study persons were impacted with exposure to a stress (a single physical exercise). It caused unidirectional hypercoagulative shifts and activation of anticoagulant and fibrinolytic blood systems. It was shown that changes of the untrained individuals' haemostatic parameters could be adjusted with preliminary administration of adaptogen - Eleutherococcus liquid ethanolic extract (1:1), 25-30 drops twice per day, 1 month course. The adaptogen administration in trained individuals resulted in disadaptive shifts in the haemostatic system. The authors concluded that these contradictory changes indicate different levels of subject's adaptive potential.

Immunomodulating effects

In vitro and *ex vivo* studies suggest an increase in leukocyte, cytotoxix T-cell, T-helper, and B- and T-lymphocyte counts in peripheral blood; in phagocytosis; in natural killer cell and T-cell activit; in stimulation of lymphocyte proliferation and activity; in interferon production; and in chemotactic migration and inhibition of migration inhibition factor (Bohn *et al.,* 1987, 1988; Kupin *et al.,* 1986b; Schmolz *et al.,* 2001; ESCOP, 2009)

A randomised, double-blind, placebo-controlled study measured the effect of an ethanol extract of the roots (1:1, standardised to contain 0.2% w/v syringin) on the immune system, using quantitative multiparameter flow cytometry with monoclonal antibodies directed against specific surface markers of human lymphocyte subsets to determine cellular immune status. 36 healthy subjects were treated orally with either 2 g of extract or placebo three times daily for 4 weeks. Subjects treated with the

extract had a significant increase in the total number of immunocompetent cells (P<0.0001), including lymphocytes (predominantly T-cells, T-helper/inducer cells and natural killer cells). A significant increase in activated T-cells was also observed (P< 0.01) (Bohn *et al.,* 1987; ESCOP, 2009).

ESCOP, 2009; cites a study (Elkin,1986) where stimulation of phagocytosis was investigated in 14 healthy volunteers who received orally 2 ml of a fluid extract of Eleutherococcus daily for 7 days, while 10 other volunteers received placebo. Blood samples for lymphocyte determination were taken before administration of the extract, on day 7 and in-follow up on day 28. The percentage of active lymphocytes was determined ex vivo by the nitro-blue tetrazolium phagocytosis test. A statistically significant increase (p<0.05) in the number of active lymphocytes was observed on days 7 and 28 (ESCOP, 2009).

Kolomievsky, 1986, studied reactions in 147 cardiologic patients with hypertension, coronary heart disease and atherosclerosis induced by 30 drops of Eleutherococcus root fluid extract over 7-10 days. The author reports an improvement of different blood count parameters (among them lymphocytes) as compared to 42 untreated controls. A statistical evaluation of the results was not carried out.

The influence of a fluid ethanolic extract was investigated on 35 healthy volunteers who received orally 75 drops of a fluid extract daily for 30 days, while 15 volunteers received pressed juice of Echinacea over the same period. The percentage of lymphocytes with spontaneous blastic transformation and phytohaemagglutinin (LF-7) induced blastic transformation as an indicator of phagocytic activity increased significantly (p<0.05) in the eleutherococcus group (by 65% and 49% respectively) but remained unchanged in the Echinacea group (Szolomicki *et al.,* 2000).

Effects on psychomotor performance, cognitive function and physical performance

The influence of an Eleutherococcus fluid extract on physical performance was investigated in 35 healthy volunteers following daily oral administration of 75 drops for 30 days. The study was randomised and active-controlled; 15 other volunteers received Echinacea pressed juice over the same period. An ergospirometric test revealed a significantly higher oxygen plateau in the Eleutherococcus group compared to the Echinacea group: oxygen consumption (litres/kg/min) during maximal effort was 39.24 before and 42.65 after 30 days, compared to 35.03 before and 36.91 after 30 days in the Echinacea group (p<0.01) (Szolomicki *et al.,* 2000).

Effects on the psychophysical one and the cognitive efficiency were examined in a placebo-controlled study of 190 pilots, co-pilots and flight engineers (helicopter occupying) in different partial groups (Gubchenko *et al.,* 1986a). The test persons received 1 ml fluid extract or placebo solution (controls) more than 10 days twice daily. The psychophysical measurements occurred before the beginning of treatment and during the 10 day of studies and in the Arctic: dynamic tremometry test, sensomotor reaction rate /reflexometer, digit-letter recognition test, menthal arithmetic test, compass selection test and a number arranging/memorising tests. Subjects in the verum group consistently demonstrated better test outcomes at the different time points compared to those in the placebo group. In several tests effects effects persisted for 3 hours (Collisson, 1991).

Arushanyan *et al.,* 2009 studied the effect of Eleutherococcus root on various psyschophysiological parameters depending on their chrontype and day time in healhy humans. It was reported that acute administration of liquid ethanolic extract (20 drops) significantly improves aural memory volume, decreases reactive anxiety and shortens individual minute. These effects were dependent on the daytime (morning verus evening) and the individual chronotype (circadian features) of each volunteer. Statistically significant efects were observed in mornings for evening people and in evenings for morning people.

The effect on experimentally induced vestibular dizziness was investigated in a controlled study involving 40 male healthy volunteers (25 had good vestibulary stability and 15 decreased vestibular stability). They were treated with 4 ml of a fluid extract 40 -60 minutes before beginning the test (swivel chair for coriolis stimulation). Swivel chair training was carried out up to the first signs of malaise, such as hot feeling, salivation or retching. Each volunteer participated in up to 30 training sessions within a period of 3 weeks. In the group with low vestibular stability 10 volunteers were treated with Eleutherococcus extract and 5 received placebo. Volunteers with good vestibular stability received no treatment and served as an additional control group. Subjects in the placebo group showed severe nausea after 7-12 minutes, while all in the Eleutherococcus group were able to support 15 minutes of swivel chair training without such reactions (ESCOP, 2009).

Eleutherococcus is reported to enhance vision and hearing. Stschichenkov, 1963, performed 60 trials to determine the influence of Eleutherococcus root on adaptation in darkness and acuteness of vision; Tikhomirova, 1977, analysed vision in seamen given adaptogens during long-term navigation. (Sosnova , 1969) determined the effect of Eleutherococcus root on the colour discrimination function in persons with normal trichromatic vision and the effect of for raising the level of the color discrimination function in railroad engineers (Sosnova & Bykova, 1976).

Sosnova *et al.,* 1984 investigated to effect of Eleutherococcus root in women performing visual control during a regime involving working with semi-conductor devices. The women were suffering from visual fatigue, followed by a significant and sharp reduction in productivity. A 40-day intake of Eleutherococcus root and Schisandra are reported to have a favourable effect on the colour discrimination capacity, to reduce fatigue, reduce the time needed for performing the main operations and to improve the quality of work and to result in a higher productivity.

In another experiment Sosnova *et al.,* 1986 has examined also a visual performance in a placebo-controlled study involving the group of healthy 232 volunteers (locomotive engineers and assistants aged 24 to 45 years). All persons had normal colour perception and visual acuity. Spectral sensitivity, colour contrast sensitivity and stability of colour perception were determined at baseline of experiment and on days 1, 5, 20 and 40 and then 2-2.5 month after the course to determine duration of the tonic effect. The treated group received 2 ml of fluid extract per day. The contrast sensitivity and the sensitivity for red, green and blue light was increased with a maximum after 5 days of treatment. After 40 days a 2.5 to 4.5 fold increase, as compared to the pre-treatment results, is reported. The effect persisted after 2.5 months. No improvement has been observed in the placebo group.

Arushanyan *et al.,* 2003 studied the effect of Eleutherococcus root on short-term memory and visual perception in healthy humans. It was reported that acute administration of liquid extract significantly improves short-term memory in healthy humans.

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

A study was conducted to assess in normal volunteers (n = 12) the influence of a standardised Eleutheroccus extract (standartised to 0.3% eleutheroside B and 0.5% eleutheroside E + ground root) on the activity of cytochrome P450 CYP2D6 and 3A4. Probe substrates dextromethorphan (CYP2D6 activity) and alprazolam (CYP3A4 activity) were administered orally at baseline and again following treatment with standardised Eleutheroccus extract (485 mg twice daily) for 14 days. Urinary concentrations of dextromethorphan and dextorphan were quantified, and dextromethorphan metabolic ratios (DMRs) were determined at baseline and after standardised Eleutheroccus extract treatment. Likewise, plasma samples were collected (0-60 h) for alprazolam pharmacokinetics at baseline and after standardised Eleutheroccus extract treatment to assess effects on CYP3A4 activity. Validated high performance liquid chromatography methods were used to quantify all compounds and

relevant metabolites. There were no statistically significant differences between pre- and post-standardised Eleutheroccus extract treatment DMRs indicating a lack of effect on CYP2D6 (P > 0.05). For alprazolam there also were no significant differences in the pharmacokinetic parameters determined by noncompartmental modeling (Cmax, Tmax, area under the curve, half-life of elimination) indicating that Eleutherococcus extract does not significantly induce or inhibit CYP3A4 (P > 0.05). The results indicate that standardised extracts of Eleutherococcus at generally recommended doses are unlikely to alter the disposition of coadministered medications primarily dependent on the CYP2D6 or CYP3A4 pathways for elimination (Donovan *et al*., 2003).

4.2. Clinical Efficacy

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

Indication - weakness, fatique

Numerous clinical studies have been performed in Soviet Union during the 1960s and 1970s (Afanasiev *et al.,* 1973; Baburin, 1966a, 1966b; Baburin *et al.,* 1970a, 1972; Baburin & Polonsky, 1970b,; Berdyshev, 1970, 1977; Blokhin, 1966; Brandis *&* Pilovitskava, 1966a, 1966b; Dalinger, 1966a, Egorov & Baburin, 1966; Gagarin, 1977; Oleynichenko, 1966). An in-depth analysis of clinical studies on Eleutherococcus root has been presented by Farnsworth *et al.,* 1985, reviewing the data available up to 1985.

In 35 clinical trials without controls, involving over 2,100 healthy subjects (4-1,000 per study), oral administration of a 33% ethanol root extract (2.0-20.0 ml, daily for up to 60 days) has been reported to improved physical and mental work performance under stress conditions, and reduced auditory disorders and the incidence of illness (Farnsworth *et al.,* 1985, Halstead *et al.,* 1984). A statistical evaluation of the results was not carried out; control groups were absent.

The effects of a 33% ethanol extract of the roots were assessed in another 35 clinical trials without controls in 2,200 patients at the age between 19 and 72 years (5-1,200 per study) with various disorders, such as arteriosclerosis (Golikov AP, 1966b; Shekhtman, 1966); acute cranio-cerebral trauma (Sandler, 1970a, 1970b, 1972a; Sandler & Sandler 1972b), hypertensive and hypotensive patients (Lyubomudrov *et al.,* 1970), neurotic patients and neurasthenia (Strokina & Mukho*,* 1966a, Strokina 1966bc, 1967); stressed drivers and factory workers (Galanova, 1977); chronic bronchitis and pneumoconiosis (Lyubomudrov *et al.,* 1971, 1972), and rheumatic heart disease (Mikunis, 1966a, 1966b). Andreev, 1976 investigated the influence of Eleutherococcus root extract on secretion, as well as on fermentative and motor functions in 18-25 years old patients with chronic gastritis.

Eleutherococcus root is reported to improve the adaptation of sailors in the tropics and influence positively body functions and the work capacity of sailors on a cruise (Berdyshev, 1970, 1977), to help adaptation to high altitudes (Kalashnikov, 1977) and in the Arctic (Gagarin, 1977; Brekhman, 1977; Kalashnikov, 1977, 1986). During long-term navigation in the tropics, where high temperature and humidity substantially restrict working capacity, sailors were given either extract of Eleutherococcus root or a placebo. It was found that Eleutherococcus root reduces mental disturbances, such as depression, excitability, insomnia etc. Eleutherococcus root is reported to have improved asthenia and depression, calmed excitability and normalised sleep. Novikov *et al.,* 1987 studied the influence of Eleutherococcus root on the body resistance in sailors and reported about the effect of Eleutherococcus root on physical exercises and on lipid metabolism in crew members of a submarine.

Brekhman, 1968a carried out experiments on more than 1,500 sportsmen.
No adverse effects were observed except for an occasional feeling of sleepiness after administration of the extract. This condition has been associated with a hypoglycemic condition. During one series of tests in 1961 and 1962, 30 male and female Olympic athletes took the extract in a dose of 2 ml 30 minutes before sleep and 4 ml one hour before training. The control group received a placebo. The group of Olympic athletes was given the extract, included sprinters, high-jumpers, decathlon contestants, 5 and 10 kilometer runners, and marathon runners. For all of them an increased endurance and the preparedness to repeat the exercises soon after completion have been reported. The control group was less active, and the restoration of pulse, arterial blood pressure, and regain of tonicity of muscles required a greater period of time.

Asano *et al.,* 1986a has investigated the effects of a preparation of Eleutherococcus root on physical performance and resources in maximal and submaximal work. A single-blind, placebo-controlled clinical trial in six baseball players assessed the effects of a 33% ethanol root extract on maximal work capacity. Three maximal work-capacity tests using a bicycle ergometer were performed on 3 consecutive days prior to treatment, and two tests were carried out after treatment with either 2 ml extract (containing 0.53 mg syringin (eleutheroside B) and 0.12 mg syringaresinol-4,-4¢-O-b-diglucoside (identified here as eleutheroside D) or placebo orally twice daily for 8 days. After each work test, maximal oxygen uptake, oxygen pulse, total work time and exhaustion time were measured. A significant improvement in all four parameters was observed in subjects treated with the extract ($P<0.01$), including a 23.3% increase in total work time as compared with only a 7.5% increase following placebo treatment.

A randomised, double-blind, placebo-controlled study was performed to examine the effect of the crude drug on submaximal and maximal exercise performance. Twenty highly trained distance runners received either a 30-34% ethanol extract of the roots (3.4 ml) or placebo daily for 8 weeks, during which they completed five trials of both 10 minute and maximal treadmill tests. Heart rate, oxygen consumption, expired minute volume, ventilatory equivalent for oxygen, respiratory exchange ratio and rating of perceived exertion were measured during both tests. Serum lactate levels were analysed in blood samples. No significant differences were observed in any of the measured parameters between the placebo and treatment groups (Dowling *et al.,* 1996).

A randomised, placebo-controlled, double-blind, crossover study compared cognitive function measurements in 24 persons who took Eleutherococcus (625 mg twice daily), Ginkgo biloba (28.2 mg flavonolglycosides daily), or placebo. At the end of each three-month dose period, concentration, selective memory, cognitive function, and well-being were measured. Significant improvements in selective memory of the Eleutherococcus group versus the placebo group ($p<0.02$) were demonstrated. For those taking ginkgo, results were significant only in persons over age 48 ($p<0.05$). No change in concentration was discovered in any group. Significant effects caused by Eleutherococcus were also noted to improve the state of wellbeing and all activity levels (Winther *et al.,* 1997).

The aim of studies by Cicero *et al.,* 2004 was to test the effect of a middle term Eleutherococcus root administration on elderly, health related quality of life (HRQOL). Twenty elderly hypertensive and digitalised volunteers (age ≥ 65 years) were randomised in a double-blind manner to Eleutherococcus root dry extract 300 mg/day ($n = 10$) or placebo ($n = 10$) for 8 weeks. After 4 weeks of therapy, higher scores in social functioning ($p = 0.02$) scales were observed in patients randomised to Eleutherococcus root; these differences did not persist until the end of the study at 8-weeks. No adverse event has been observed in both groups of patients. No significant difference in both blood pressure control and digitalemia was observed in both treatment groups. Persons given Eleutherococcus root have received more active therapy than persons given placebo (20%, $p < 0.05$). The authors conclude that Eleutherococcus root safely improves some aspects of mental health and social functioning after 4 weeks of therapy, although these differences attenuate with continued use.

Hartz *et al*., 2004 conducted a 2-month, randomised, blinded and controlled trial of Eleutherococcus root in patients with chronic fatigue. Ninety-six subjects were randomised to treatment groups, and 76 provided information at 2 months of follow-up. Fatigue among subjects assigned to either placebo or *Eleutherococcus senticosus* (standartised extract from root, providing 2.24 mg eleutherosides B and E daily), was substantially reduced during the study, but differences between treatment groups were not statistically significant. It was concluded that overall efficacy was not demonstrated. However, the findings of possible efficacy in a subgroup of patients with moderate fatigue suggest that further research may be of value.

Kuo *et al.,* 2010: The aim of the study was to examine the effects of *Eleutherococcus senticosus* (ES) supplementation on endurance capacity, cardiovascular functions and metabolism of recreationally trained males for 8 weeks. Nine recreationally trained males in college consumed 800 mg/day of ES (root or rhizome, extraction solvent not specified, contains 0.11% eleutheroside B and 0.12% eleutheroside E (HPLC)) or starch placebo (P) for 8 weeks according to a double-blind, randomised, placebo controlled and crossover design with a washout period of 4 weeks between the cycling trials. Subjects cycled at 75% V˙ O2 peak until exhaustion. The examined physiological variables included endurance time, maximal heart rate during exhaustion exercise, V˙ O2, rating of perceived exertion and respiratory exchange ratio. The biochemical variables including the plasma free fatty acid (FFA) and glucose were measured at rest, 15 min, 30 min and exhaustion. The major finding of this study was the V˙ O2 peak of the subjects elevated 12% ($P < 0.05$), endurance time improved 23% ($P < 0.05$) and the highest heart rate increased 4% ($P < 0.05$) significantly. The second finding was at 30 min of 75% V˙ O2 peak cycling, the production of plasma FFA was increased and the glucose level was decreased both significantly ($P < 0.05$) over 8-week ES supplementation. The authors conclude that this is the first well-conducted study that shows that 8-week ES supplementation enhances endurance capacity, elevates cardiovascular functions and alters the metabolism for sparing glycogen in recreationally trained males.

Schaffler *et al.,* 2013: Multicenter, phase IV study was designed as a prospective, exploratory, open, controlled, randomised 3-arm parallel group comparison of 3 treatment schedules: participation in a 2-day professional stress management training (SMT); oral treatment with 120 mg/day *Eleutherococcus senticosus* root dry extract (ES, 16-25:1, ethanol 30%v/v), and a combination of both (COM). 144 participants suffering from asthenia and reduced working capacity related to chronic stress were randomised to the treatments. Validated scales and tests were used to investigate cognitive performance; feeling stressed; fatigue and exhaustion; alertness, restlessness and mood; quality of life and sleep; physical complaints and activities; and physiological stress parameters including cortisol awakening response (CAR), at baseline, after 2 and 8 weeks of treatment. Results: almost all parameters improved significantly over time without group differences. Significant differences were found in mental fatigue and restlessness, both in favor of COM vs. ES. COM was not superior to SMT in any parameter at week 8. An attenuation of the CAR was seen at week 2 without group differences. All treatments were well tolerated. The authors conclude that effects of adding *Eleutherococcus senticosus* root extract to stress management training are, if any, negligible.

Other indications

Several experiments carried out in the Soviet Union during the 1970s appear to demonstrate that Eleutherococcus root extract, given prophylactically, can reduce the overall disease incidence by up to 35% (Galanova, 1977; Schezin *et al.,* 1977; Kalashnikov, 1977).

Shadrin *et al.,* 1986; have reported results of estimation of prophylactic and immunostimulating effects of Eleutherococcus preparations. The prophylactic effect of the Eleutherococcus liquid extract compared with influenza virus infections and other acute respiratory illnesses was examined in a controlled study

double-blind including 1376 persons. A half of the persons received 2 ml fluid extract once daily at the beginning and during the influenza virus epidemic, another half received placebo. Typical complications of an influenza infection, like pneumonia, bronchitis, genyantritis and otitis were determined. Morbidity rates were determined during the all treatment period and in a 3-months long postobservation period, and were consistently lower in the Eleutherococcus group than in the placebo group, but the differences were not statistically significant. Nevertheless administration of Eleutherococcus led to a significantly lower frequency of complications caused by infections ($p<0.05$), thus indicating milder infection development.

The effect of Eleutherococcus on respiratory viral infectious morbidity in children in organised collectives has been studied. The search involved 764 children 1-7 years old, 395 of them having received Eleutherococcus liquid extract (no further details reported) for a month. As a result the morbidity rate decreased 3.6 times in those treated with Eleutherococcus. After 2 years the investigation was repeated in 265 children. The 2 -3 fold decrease of morbidity was recorded in those receiving Eleutherococcus liquid extract for a month comparing to the control group of 252 children (Barkan *et al.,* 1980). Another study investigated the effect of preventive administration of Eleutherococcus extract on health of children at pre-school age. As a result in different pre-schools the morbidity rate decreased by 30-40% (Sheparev *et al.,* 1986).

ESCOP ,2009; cites a double-blind, placebo-controlled study performed by Williams,1995, where 93 patients were treated orally with 400 mg of Eleutherococcus root dry extract (standardised on Eleutherosides B and E; reported as equivalent of 4 grams of dried roots) or placebo daily for 6 months as a prophylactic treatment to recurrent episodes of *Herpes simplex type* II infections. Based on questionnaires (covering the 6 months before treatment and after 6 months of treatment), 75% of patients in the Eleutherococcus root group reported an improvement in the frequency, severity and duration of outbreaks compared to 34% in the placebo group; the results were significant in favour of the verum group ($p = 0.0002$ to 0.0007).

Li *et al.,* 2009; in Cochrane systematic review assessed the efficacy and safety of Eleutherococcus in patients with acute ischemic stroke. Authors included 13 randomised controlled trials (962 participants); the period of follow up in all included trials ranged from 10 to 30 days. None of the trials reported the pre-specified primary outcome death or dependency during the follow-up period. The outcome measure in all included trials was the improvement of neurological deficit after treatment; Eleutherococcus was associated with a significant increase in the number of participants whose neurological impairment improved (risk ratio (RR) 1.22, 95% confidence interval (CI) 1.15 to 1.29). Two trials reported adverse events; five trials reported no adverse events. The authors concluded that the risk of bias in all the included trials was high, and hence the data were not adequate to draw reliable conclusions about the efficacy of Eleutheroccus in acute stroke. Much larger trials of greater methodological quality are needed.

Data from combinations

Park *et al.,* 2009: A so-called 'anti-inflammatory factor' (AIF) is a water soluble extract of three herbs, Panax notoginseng (Burk.) F. H. Chen, Rehmannia glutinosa Libosch and *Eleutherococcus senticosus*. The study aimed to investigate the safety and efficacy of AIF on Korean knee osteoarthritis patients for six weeks. Two capsules each of AIF (Each capsule contains; 400 mg of mixture, include eleutheroside E 0.07±0.014 mg/g) and similar identical placebo were administered twice a day to both groups. Pain intensity at second, fourth, and sixth weeks of study as well as one week after discontinuation of drugs was assessed. Results showed an improvement in the physical function of Korean version of the Western Ontario and McMaster Universities K-WOMAC scale which was significantly higher ($p=0.013$) in AIF than placebo group, and decreases of total K-WOMAC score were also significantly higher

(p=0.030) in AIF groups than placebo group. No serious adverse effect was observed, and there was no difference in incidence of adverse effect between AIF and placebo groups. AIF was found to be safe, tolerable and effective for symptomatic improvement of pain and physical function.

Aslanyan *et al.,* 2010: The aim of this study was to assess the effect of a single dose of ADAPT-232 (a standardised fixed combination of *Rhodiola rosea* L., *Schisandra chinensis* (Turcz.) Baill., and *Eleutherococcus senticosus* Maxim. (10.5:1; extraction solvent 70% ethanol, standartised with respect to eleutherosides B and E 0.15%) extracts on mental performance, such as attention, speed and accuracy, in tired individuals performing stressful cognitive tasks. The effects of the extract were measured prior to treatment and two hours after treatmentand showed a significant difference ($p<0.05$) in attention, speed, and accuracy between the two treatment groups. The subjects in the ADAPT-232 group quickly (two hours after verum was taken) gained improved attention and increased speed and accuracy during stressful cognitive tasks, in comparison to placebo. There was also a tendency of ADAPT-232 to reduce percentage of errors, which means better accuracy, quality of the work, and degree of care in the volunteers under stressful conditions. No serious side effects were reported, although a few minor adverse events, such as sleepiness and cold extremities, were observed in both treatment groups.

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

Children

Only a few studies have tested the effect of Eleutherococcus root in children.

Effect of Eleutherococcus root on respiratory viral infectious morbidity in children in organised collectives has been studied by Barkan *et al.,* 1980.

Sheparev *et al.,* 1986; investigated the effect of preventive administration of Eleutherococcus root extract on the health of children under school age. The morbidity rate is reported to have decreased by 30-40%.

Vereshchagin, 1978; Vereshchagin *et al.,* 1982; have studied the effect of adaptogens on antibiotic therapy in children aged 0-14 years suffering from dysentery and Proteus infections.

No clear information on posologies in children of different age groups can be taken from these studies. The use of Eleutherococcus root is generally not recommended in children below the age of 12 years.

Elderly

Turkewicz & Daniljuk, 1966a; Turkewicz *et al.,* 1966b; analysed the results with Eleutherococcus root or Eleutherococcus leaves liquid extracts (no futher details reported) in the treatment of patients with psychosis in the elderly and atherosclerotic psychoses. Patients at the age between 65 and 90 years were given 5-15-20 drops daily 30 minutes before food, the treatment lasted 1 month, then it was repeated, after a 10 days break, 2 to three times. It is reported that the number of patients with psychopathological symptoms: asthenia, depression, tension, mental deficiency, had been reduced and that biochemical parameters were improved. Normalisation of all biochemical parameters did coincide with improved clinical symptoms.

Davydov & Krikorian 2000; reported that Eleutherococcus root improves self-reported quality of life in elderly, without affecting their blood pressure control. Similar results were described in young healthy adults (Asano *et al.,* 1986b).

Cicero *et al.,* 2004; in his study tested the effect of a middle term Eleutherococcus root administration on elderly hypertensive and digitalised volunteers (age ≥ 65 years) (see section 4.2.2.).

4.3. Overall conclusions on clinical pharmacology and efficacy

Numerous clinical studies on Eleutherococcus preparations have been conducted since 1960s. In most of the studies, results were generally reported to be positive: e.g. blood pressure was normalised, serum prothrombin and cholesterol levels were reduced, and overall wellbeing and physical work performance improved (Farnsworth *et al.,* 1985). However, these trials lacked good methodology (for example, very few patients were involved, lacked proper controls and randomisation, experiments were not double-blind etc.). The clinical data have a number of shortcomings such as deficiencies in the description of inclusion and exclusion criteria, description of the medication, diagnosis, study design, analysis etc. There is a wide range of clinical conditions that have been investigated and in some studies the number of patients was very small. The beneficial effects of Eleutherococcus (enhances endurance capacity, elevates cardiovascular functions and alters the metabolism for sparing glycogen) was found in more recent study by Kuo *et al.,* 2010 after 8 weeks treatment. However, too small number of participants does not allow deducing an evidence of clinical efficacy. The clinical study performed by Schaffler *et al.,* 2013 showed that addition of *Eleutherococcus senticosus* root extract to stress management did not created any substancial effect.

In conclusion, none of the studies would be sufficient to substantiate efficacy of Eleutherococcus preparations in a clearly defined clinical condition, although, in total, the data available are sufficient to justify further research into the concept of adaptogens.

Brekhman, 1968a has coined the term “adaptogen” to designate substances which in a non-specific way: increase protein biosynthesis; raise antibody titre at immunisation; elevate the body’s metabolic capacity by means of general endocrine stimulation; enhance mental work capacity; uplift physical work capacity along with performance and endurance; quench free radicals; improve senses such as eyesight, colour perception, hearing and vestibular functions; offer beneficial effects in cardiovascular and respiratory systems; promote longevity; heighten the body’s non-specific resistance to various stressors such as toxins, excess cooling, overheating, altered barometric pressure, ultraviolet, ionising radiation. Adaptogens must present a non-specific effect (raising the power of resistance to toxins of a physical, chemical or biological nature); must be harmless and disturb the body functions as little as possible. Accordingly, adaptogens are expected to strengthen the non-specific powers of resistance to non-infectious stresses, raise the general performance capacity during stress situations, and thereby prevent diseases that could develop as a result of over-stressing the organism.

There are numerous studies intended to support the adaptogenic nature of Eleutherococcus root extracts in both animal models and humans. Although many clinical studies have been published, most of them are not of appropriate quality and does not prove the efficacy of the Eleutherococcus root in a well-defined clinical condition. This may be linked to the fact that the main intention has been to prove the adaptogenic concept and not the effect in the prevention or treatment of a well-defined disease. Whereas the term "adaptogen" is widely used and generally accepted in some countries, it is completely unknown or badly understood in many others. The term is absent from standard (western) handbooks such as Goodman and Gilman's The Pharmacological Basis of Therapeutics or Harrinson's Principles of Internal Medicine.

Despite the great number of studies, Eleutherococcus root preparations do not reach the level of WEU/scientific evidence that would be sufficient to grant a marketing authorisation. However, the studies provide a solid basis for plausibility of the traditional use. Please refer to the HMPC reflection paper on the adaptogenic concept (EMEA/HMPC/102655/2007) for an in depth discussion.

5. Clinical Safety/Pharmacovigilance

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

In general, only minimal adverse events have been reported. Systematic studies that were designed to detect adverse events are absent. Case reports and general evidence point to the following effects: Eleutherococcus root may cause insomnia in some people if taken too close to bedtime. In the study involving atherosclerotic patients, some cases of insomnia, shifts in heart rhythm, tachycardia, extrasystoles were reported (Golikov AP, 1966b).

Another study involving 55 patients with rheumatic heart disease (Mikunis *et al.,* 1966a, 1966b), showed that 2 of the patients out of 55 (at high dose levels of the extract) reported headaches, pericardial pain, palpitations, and elevated blood pressure.

Another study (Koshkareva *et al.,* 1966), involving 11 patients diagnosed as hypochondriacs, reported that the Eleutherococcus root extract was well tolerated at dose levels of 2.5-3.0 ml three times daily for 60 days, but some patients often presented insomnia, irritability, melancholy and anxiety at dose levels of 4.5-6.0 ml.

In randomised double-blinded study with 20 elderly hypertensive and digitalised volunteers receiving Eleutherococcus root dry extract 300 mg/day for 8 weeks no adverse events has been observed (Cicero *et al.,* 2004).

In the study, which comprised 40 patients treated with 500 mg Eleutherococcus extract (extraction solvent not known) for 6 months, no adverse effects were reported (Lee *et al.,* 2008).

In the 2-month, randomised, blinded, controlled trial with 96 patients (receiving standartised extract from root that contains 2.24 mg eleutherosides B and E daily) with chronic fatigue some side effects were reported, such as nervousness, headache, breast tenderness and other. However, the rates of side effects were similar for patients assigned to Eleutherococcus and those assigned to placebo (24% and 28% respectively). There was a higher (but not significantly different) rate of breast tenderness and uterine bleeding in the intervention than in the control group (14% versus 4% respectively). The authors also tested whether blood pressure was affected by Eleutherococcus. The mean change in systolic blood pressure from baseline to 1 month visit was 0.97 for the placebo subjects and -0.93 for the subjects on Eleutherococcus. The respective changes in diastolic blood pressure were -0.48 and -0.37. Neither of these differences were statistically different (Hartz *et al.,* 2004).

No adverse reactions were reported in the double-blind, randomised, placebo controlled study where 9 patients received 800 mg/d of *Eleutherococcus senticosus* extract (root or rhizome, extaction solvent not specified, contains 0.11% eleutheroside B and 0.12% eleutheroside E (HPLC) for 8 weeks (Kuo *et al.,* 2010).

In the study that explored the effects of 120 mg/day *Eleutherococcus senticosus* root extract (DER 16-25:1, ethanol 30%v/v) in 144 participants, the treatment was well tolerated (Schaffler *et al.,* 2013).

5.2. Patient exposure

No exact data on patient exposure are available. In clinical investigations of more than 20,000 patients and test persons no signs of acute toxicity have been observed (Fulder, 1980). On the basis of the wide-spread use in some Member States over a period of more than 30 years a significant exposure can be assumed.

5.3. Adverse events and serious adverse events and deaths

Adverse events

Information on adverse events is inconsistent. See section 5.1.

The following adverse reactions have been reported in a few studies (all performed in 1966): insomnia, shifts in heart rhythm, tachycardia, extrasystoles, palpitations, headache, pericardial pain, elevated blood pressure, irritability, melancholy and anxiety. In the study performed by Hartz *et al.,* 2004 nervousness, headache, breast tenderness and uterine bleeding was mentioned, however, the differences between test and placebo group were negligible (see 5.1).

The 'Botanical Safety handbook' mentions insomnia as side effect rarely observed in association with clinical studies (Mc Guffin *et al.,* 1997). The '*Essential guide to herbal safety'* reports that insomnia, palpitations, headache, tachycardia, pericardial pain and hypertension have been reported in a few cases in patients with cardiovascular disorders. Furthermore, side effects are more likely if normal doses are exceeded (Mills *et al.,* 2005).

ESCOP, 2009; states that none of undesirable effects is confirmed. According to Blumenthal *et al.,* 1998, no side effects are known.

In the more recent clinical studies no side effects were reported (Cicero *et al.,* 2004; Lee *et al.,* 2008; Kuo *et al.,* 2010; Schaffler *et al.,* 2013).

Information regarding combinations

There is a report of spontaneous subarachnoidal hemorrhage in a 53-year old woman associated with the use of a multicomponent herbal supplement containing *Eleutherococcocus senticosus* root (76 mg per 2 tablets/daily) together with Wild yam, Black cocosh, Red clover, Don quai, Raspberry leaf, Vitex, Partridge berry and nettles leaf. The authors conclude that Red clover, Don quai and Siberian ginseng as source of coumarins might be the possible cause of this case (Friedmann *et al.,* 2007).

In the review of spontaneously reported adverse reactions in association with complementary and alternative medicine substances in Sweden amoung 64 493 reports (submitted between 1987 and 2006), 57 reports concerned combination product consisting of *Echinacea purpurea* + *Eleutherococcus senticosus* + *Adhatoda vasica*. Urticaria, angioedema, anaphylactic reaction, exathema, increased hepatic enzymes, fever were among reported adverse reactions (Jacobsson *et al.,* 2009).

Currently the following side effects are mentioned in the monograph and list entry: "Insomnia, irritability, tachycardia and headaches may occur. The frequency is not known". During the 5-year review no new data regarding side effects were identified. Data from combinations do not allow to draw any new conclusions with respect to Eleutherococcus safety. Therefore, no amendments are required in the monograph and list entry in this respect.

Serious events and deaths

None known for Eleutherococcus root preparations administrated orally.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Use in pregnancy and lactation

Effects on fertility or effects during lactation have not been reported for humans (Sonnenborn *et al.,* 1993).

In a therapy accompanying investigation in 619 pregnant women with a high risk for a prenatal dystrophy no teratogenic or embryo-toxic effects (Bolkhovitinova *et al.,* 1981) were observed with a prophylactic interval therapy about 3 weeks three times daily by 20 to 30 drops of the fluid extract of Eleutherococcus root.

Bolkhovitinova, 1986 investigated the influence of Eleutherococcus root on pregnancy termination for mother and on the fetus in 1770 pregant women with a high risk of fetal hypotrophy. . The most favourable pregnance outcome was observed in women who received therapy of 3 weeks three times daily by 20 to 30 drops of the fluid extract of Eleutherococcus root in 3 courses (8-10, 18-20, 28-30 weeks of pregnancy).

A few sources (Mc Guffin *et al.,* 1997; Gardner *et al.,* 2013; Mills *et al.,* 2005) report a case of neonatal androgenisation which was attributed to maternal use of “pure Siberian ginseng”. Further follow-up research revealed that this product was adulterated with *Periploca sepium* (Awang, 1996).

No teratogenic or other effects have been observed in available studies on animals. However, adequate clinical data are lacking, therefore safety during pregnancy and lactation has not been fully established. In accordance with general medical practice and in absence of sufficient data, Eleutherococcus root should not be used during pregnancy and lactation.

Drug interactions

Several sources (McRae, 1996; Williamson, 2003; Mills *et al*., 2005; Barnes *et al*., 2007; Huang *et al*., 2011a) report the case of raised serum digoxin concentrations in a 74–year old man who had been taking a constant dose of digoxin for many years and was found to have an elevated serum digoxin level with no signs of toxic effects (5.2 nmol/l against previous stable range 0.9 to 2.2 nmol/l). Common causes of elevated serum digoxin were ruled out, and the patient's digoxin level remained high after digoxin therapy was stopped. The patient then revealed that he was taking Eleutherococcus (duration for use not specified but at least 2 months). The patient stopped taking Eleutherococcus, and the serum digoxin level soon returned to an acceptable level. The digoxin therapy was resumed. The patient resumed taking Eleutherococcus several months later, and the serum digoxin level again rose. Digoxin therapy was maintained at a constant daily dose, the Eleutherococcus was stopped once more, and the serum digoxin levels again returned to within the therapeutic range. It is not stated in the report whether the patient took the same or different Eleutherococcus product during the second espisode of use. Also the researchers failed to test for eleutherosides to authenticate the product. For this reason the validity of this report has been questioned, indicating that the product may have been adulterated with *Periploca sepium*, an herb that contains cardioactive glycosides (McRae, 1996; Barnes *et al*., 2007; Awang, 1996; Gardner *et al*., 2013).

The elevated digoxin levels may be due to an interference with the digoxin immunoassay (due to the structural similarity between Eleutherococcus glycosides and digoxin), especially since no toxic effects of elevated digoxin were observed. However, such high interference (almost 3 fold increase) of Eleutherococcus with the digoxin assay methods was not confirmed in the study performed by Dasgupta, 2008b.

It was observed that Eleutherococcus interferes moderately with digoxin measurements. Eleutherococcus showed falsely elevated digoxin values using FPIA, falsively decreased values using the microparticle enzyme immunoassay (MEIA), no interference with the EMIT (enzyme multiplied immunoasssay, turbidimetric, chemiluminesscent assay (CLIA), Tina quant and Syncron LX system (Dasgupta *et al*., 2003; Dasgupta, 2008b). In the subsequent studies the modest apparent digoxin concentrations and falsively elevated digoxin concentrations using Digoxin III assay were observed (Dasgupta *et al*., 2008a), whereas no measurable interference was observed using homogeneous sequential chemilumiscent assay (LOCI digoxin) (Dasgupta *et al*., 2011).

It has been reported that Eleutherooccus preparations do not affect CYP3A4 and CYP2D6 activity (Donovan *et al*., 2003). According to the study of Takahashi *et al*., 2010, Eleutherococcus *in vitro* inhibits drug transport mediated by P-glycoprotein and the inhibition is due to a non-competetive mechanism. Therefore, when such drugs and Eleutherococcus are concomitantly used, the blood level of the drugs might be affected. It was concluded, whereas the mechanism of drug-drug interaction after concomitant interaction of digoxin and Eleutherococcus extract remains unclear, the inhibition by constituents of Eleutherococcus of the transport activity of P-glycoprotein may be involved. No further *in vivo* or clinical studies could be found in this respect.

In the review of the risk of drug interaction in the cardiovascular pharmacotherapy and herbal medicines, Izzo *et al*., 2005 reports increased plasma digoxin concentrations (some component might impair digoxin elimination or interfere with the digoxin assay) and refers to the case reported by McRae, 1996.

Heinrich *et al*., 2008 in his review confirms low risk of Eleutherococcus interactions by assessing clinically relevant interactions with the cytochrome P450 enzyme systems of herbal extracts used for upper respiratory tract infections.

Barnes *et al*., 2007; concludes that taking into account the constituents and pharmacological actions of Eleutherococcus preparations and their constituents, the potential interaction with other medicines administered concurrently, particularly those with anticoagulant, hypoglycaemic and /or hypo/hypertensive activity should be considered.

Overdose

From literature, monographs and databases of the Member States, no case reports on overdose of Eleutherococcus root preparations are available.

Drug abuse

No reports identified.

Withdrawal and rebound

No reports identified.

Effects on ability to drive or operate machinery

No studies on the effect on the ability to drive and operate machines have been published.

Contraindications

Known hypersensitivity to the active substance or to Araliaceae (WHO, 2002). However, literature that points to the occurrence of a general hypersensitivity to Araliacea has not been found.

Controversial information regarding arterial hypertension as contraindication can be found in literature. Arterial hypertension as contraindication is stated in reviews (Farnsworth *et al.,* 1985; Bleakney, 2008) and monographs (Blumenthal *et al.,* 1998; Duke *et al.,* 2002; McGuffin *et al.,* 1997; Mahady *et al.,* 2001; WHO, 2002; Aicher *et al.,* 2006). Barnes *et al.,* 2007 mentions that Eleutherococcus is unsuitable for individuals with high blood pressure (180 mm/Hg or higher). Mills *et al.,* 2005 states that some medical scientists and expert bodies consider it to be contraindicated in hypertension, but it also been used to treat hypertension. ESCOP, 2009; Mashkowsky, 1997; indicates no known contraindications.

All of these reviews and monographs regarding contraindicated arterial hypertension refer directly or indirectly (Farnsworth *et al.,* 1985) to publications of Dalinger,1966b; Lapchik, 1967. Dalinger, 1966b has published a study conducted in 35 workers (aged 53-74). Twentyfour of the participants were hypertonic with systolic values in the range 135-164 mm Hg, one participant had blood pressure values 180/90 mmHg. It was concluded that after the treatment with 25-30 drops of Eleutherococcus liquid extract twice daily for 12 days, improvement was noted in parametres of the cardiovascular system and in the ability to work in older patients without marked hypertension. It is mentioned that systolic values in patients with initial hypertension 135-164 mm Hg lowered by 12.4 mm on average, diastolic values – by 5.3 mm Hg. In five participants blood pressure did not change. In one patient with hypertension and Parkinson, use of Eleutherococcus was stopped due to increased sleepiness and dizziness. Dalinger concludes that use in patients with arterial hypertension (more than 180/90 mm Hg) is not useful. In review of Farnsworth *et al.,* 1985 the conclusion of the Dalinger study is translated/reported as “it was recommended that the extract not to be given to subjects having blood pressure in excess of 180/90 mmHg”. This has been further used as the reference for justification of contraindication in several reviews and monographs. Taking into account the content of original publication, the appropriateness of the study of Dalinger for justification of contraindication “arterial hypertension” has been questioned (Schmidt, 2013).

A study of Lapchik, 1967 does not refer to the clinical use of Eleutherococus and should not be taken into account.

In the publication of Golikov AP, 1966b, arterial hypertension with high level of blood pressure (no exact values) is stated as relative contraindication. However, no increase of blood pressure was reported in this study that could serve as a justification of such statement.

No side effects with respect to the elevated blood pressure have been reported in more recent clinical studies or spontaneous reporting schemes.

Taking into account the above mentioned considerations, during the 5-year revision it was decided to remove the contraindication “Arterial hypertension” from the monograph and list entry.

5.6. Overall conclusions on clinical safety

The oral administration of Eleutherococcus root preparations can be regarded as safe under the conditions of use that are described in the monograph/list entry. Preparations of Eleutherococcus root intended for adults and adolescents over 12 years of age have been on the market in the Member States for more than 30 years without any indication of serious risks. In general, only minimal adverse events have been reported. Reported adverse effects include insomnia, irritability, tachycardia and headache.

There is one case report that describes elevated serum digoxin level when used concomitantly with Eleutherococcus preparation. However, the validity of the report has been questioned, as the identity of the used preparation was not clearly stated. The elevated digoxin levels might be due to an interference with the some digoxin immunoassay methods, however this requires further investigation.

Studies in healthy human volunteers showed no clinical relevant impact on CYP2D6 or CYP3A4 pathways for elimination. Recent *in vitro* studies have shown that Eleutherococcus inhibits drug transport mediated by P-glycoprotein and the peptide transporter and that could lead to impaired digoxin elimination. No further *in vivo* or clinical investigations are available regarding this issue.

During the 5-year revision it was decided to remove the contraindication “Arterial hypertension” from the monograph and list entry as no clear justification can be deducted from literature and no side effects with respect to the elevated blood pressure have been reported in clinical studies or spontaneous reporting schemes.

No adequate data are available on use in children below the age of 12 years, therefore Eleutherococcus root cannot be recommended in this age group.

No teratogenic or other effects have been observed in available studies on animals. However, adequate clinical data is lacking, therefore safety during pregnancy and lactation has not been fully established. In accordance with general medical practice and in absence of sufficient data, Eleutherococcus root should not be used during pregnancy and lactation.

6. Overall conclusions

Preparations from *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim. root have been traditionally used for many decades as a tonic for the relief of symptoms in case of decreased performance such as fatigue and sensation of weakness, exhaustion, tiredness and loss of concentration, also as a prophylactic and restorative tonic for enhancement of mental and physical position, and as adaptogen to increase body resistance to such stressful exposures. The period of at least 30 years of medicinal use including at least 15 years within the European Union as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product is documented for the following preparations:

1. Comminuted herbal substance
2. Powdered herbal substance
3. Liquid extract (1:1), ethanol 30-40% v/v)
4. Dry extract (13-25 : 1, ethanol 28-40% v/v)
5. Dry extract (17-30 : 1, ethanol 70%, v/v)
6. Dry aqueous extract (15-17:1)
7. Tincture (1:5, ethanol 40% v/v)
8. Liquid extract (1:11), sweet wine
9. Liquid extract (1:20), sweet wine

Traditional use for symptoms of asthenia such as fatigue and weakness is considered plausible on the basis of long-standing use and the outcome of the numerous pre-clinical and clinical investigations.

Despite the high number of studies, Eleutherococcus root preparations do not reach the level of well-established use. The clinical data is still inconclusive and strong evidence for clinical efficacy cannot be deducted.

Based on long-standing use and outcome of clinical investigations no specific safety concern arises. Reported adverse effects include insomnia, irritability, tachycardia and headache. Possible interference of Eleutherococcus with some digoxin immunoassay methods is reported, requiring further investigation. No other interaction mechanisms have been proven.

Oral administration of Eleutherococcus root can be regarded as safe at traditionally described and used doses in adults and adolescents over 12 years of age.

Due to the lack of adequate data, Eleutherococcus root is not recommended in children below 12 years of age, in pregnancy and lactation.

Duration of use: Not to be taken for more than 2 months. If the symptoms persist for more than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Eleutherococcus root aqueous and ethanolic extracts in AMES assay test with *Salmonella typhimurium* strains TA 100 and TA 98 and in the micronucleus test in mice showed a negative outcome. Although there is one of the strains of *Salmonella typhimurium* lacking in the published AMES test, negative outcome in in-vivo micronucleus test can be regarded as sufficient for the development of list entry for Eleutherococcus root aqueous and ethanolic extracts.

Following preparations are included in the Community list:

1. Comminuted herbal substance
2. Liquid extract (1:1), ethanol 30-40% v/v)
3. Dry extract (13-25 : 1, ethanol 28-40% v/v)
4. Dry extract (17-30 : 1, ethanol 70%, v/v)
5. Dry aqueous extract (15-17:1)
6. Tincture (1:5, ethanol 40% v/v).

Annex

List of references