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SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Rhodiola rosea* L., rhizoma et radix

Final – Revision 1

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)		*Rhodiola rosea* L., rhizoma et radix
Herbal preparation(s)		Dry extract (DER 1.5-5:1), extraction solvent ethanol 67-70% (V/V)
Pharmaceutical forms		Herbal preparations in solid dosage forms for oral use.
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1. Introduction

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

- Herbal substance(s)

The herbal substance consists of the dried roots and rhizomes of *Rhodiola rosea* L., (*Crassulaceae)*. Although the plant part in use is commonly referred to as the root, the anatomy of these parts reveals that these parts are underground stems (rhizomes) with irregular secondary thickening. The plant is native throughout the mountains in the Northern Hemisphere. A main source of commercially available rhizomes is the Altai region in Asia (Panossian *et al.,* 2010a).

Common names are Roseroot, Rosenroot, Golden Root, Arctic Root, Rosenwurz. The name refers to the rose-like fragrance of the fresh cut underground organs.

Constituents (according to Panossian *et al.,* 2010a, Ali *et al.,* 2008, Tolonen *et al.,* 2003):

Phenylalkanoids: Phenylethanoids (e.g salidroside [Syn. rhodioloside]: p-hydroxyphenylethyl-O-ß-D-glucopyranoside), phenylpropenoids (e.g. rosin: cinnamyl-O-ß-D- glucopyranoside; rosarin: (cinnamyl-(6'-O-α-L-arabinofuranosyl)- O-ß-D- glucopyranoside; rosavin: (cinnamyl-(6'-O- α-L-arabinopyranosyl)- O-ß-D- glucopyranoside), phenylpropanes (e.g. tyrosol). Only limited data are available regarding the quantitative composition. Hellum *et al.,* 2010 report a considerable variability between clones of *Rhodiola rosea* in Norway based on data obtained from ethanolic extracts (primary extraction solvent ethanol 96%). Irrespective of the plant origin (cultivated in Lithuania or naturally occurring in Altai Mountains) Kucinskaite *et al.* (2007) found in aqueous-ethanolic extracts 1.35-1.62 mg/ml of salidroside, while the profile of rosavines differed considerably. Ethanol 70% V/V yields extracts with a low content of salidroside compared to ethanol 40% V/V; in contrast rosavins are more efficiently extracted by ethanol 70% (Kucinskaite *et al.,* 2007).

Essential oil: The dried rhizome contains approximately 0.05% of essential oil. Main components are α-pinene, geraniol, limonene, ß-phellandrene, linalool, n-octanol, n-decanol, dodecanol, 1,4-p-menthadien-7-ol and cumin alcohol (Rohloff 2002). Evstatieva *et al.* (2010) found considerable differences in the composition of the essential oil of different origin. In a sample from Bulgaria, myrtenol and meraniol counted for more than 75%; in an Indian sample phenethylalcohol was the main component (56%); in a sample from China, geraniol (57%) and n-octanol were the dominating components.

Monoterpene derivatives: rosiridol, rosiridin, rhodiolosides A-E.

Cyanogenic glycosides: rhodiocyanoside A, lotaustralin

Proanthocyanidines: prodelphinidine-gallate esters

Flavonolignans: rhodiolin

Flavonoids: *Rhodiola*-specific flavonoids like rhodionidin, rhodiolgin, rhodalidin, rhodionin, rhodiolgidin, rhodalin, rhodiosin; tricin and kaempferol derivatives.

Phenolic acids: chlorogenic acid, hydroxycinnamic acid

- Herbal preparation(s)

Dry extract (DER 1.5-5:1), extraction solvent ethanol 67-70% V/V

- 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.

Not applicable.

1.2. Search and assessment methodology

The searches have been performed in July 2021.

Search term: *Rhodiola rosea*

Databases: Pubmed, Medline, Toxnet, EudraVigilance data base.

Libraries: University Vienna, centre of pharmacy; Medical University Vienna, central library.

1.3. Main changes introduced in the first revision

During the first revision new information on possible interactions and undesirable effects was found and assessed. Moreover the wording of the indication for the monographs was slightly adapted. The assessment report has been updated with relevant new references. Some references were considered not relevant during the first revision and were deleted.

2. Data on medicinal use

2.1. Information about products on the market

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

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
Dry extract (1.5-5:1), extraction solvent ethanol 60% m/m	Traditionally used for the temporary relief of symptoms of stress, such as fatigue and sensation of weakness.	Film-coated tablet *Adults:* SD 200 mg DD 400 mg If the symptoms persist longer than 2 weeks during the use of the medicinal product or worsen, a doctor or a person qualified in medical heath care should be consulted.	TUR since 2014, DE
Dry extract (1.5-5:1); extraction solvent ethanol 70% (V/V)	Traditional herbal medicinal product for temporary relief of symptoms of stress,	Film-coated tablet *Adults:* SD 200 mg DD 400 mg	TUR since 2016, DE

Active substance	Indication	Pharmaceutical form	Regulatory Status
	such as fatigue and sensation of weakness in adults.	If the symptoms persist longer than 2 weeks during the use of the medicinal product or worsen, a doctor or a person qualified in medical heath care should be consulted.	
Dry extract (3.5:1); extraction solvent ethanol 70% (V/V)	Convalescence	Coated tablet Adults: SD 145 mg DD 145-290 mg	24.10.2001, DK
Dry extract (1.5-5:1), extraction solvent ethanol 60% m/m	THMP for the temporary relief of symptoms related to stress such as fatigue and weakness.	Film-coated tablet *Adults:* SD 200 mg DD 400 mg If the symptoms persist longer than 2 weeks during the use of the medicinal product or worsen, a doctor or a person qualified in medical heath care should be consulted.	TUR, 05.2010, ES
Dry extract (1.5-5:1), extraction solvent ethanol 67.7% V/V	Traditional herbal medicinal product for temporary relief of symptoms of stress, such as fatigue, mental exhaustion and mild anxiety state.	Film-coated tablet *Adults:* SD 200 mg DD 400 mg If the symptoms persist longer than 2 weeks during the use of the medicinal product or worsen, a doctor or a person qualified in medical heath care should be consulted.	TUR, 2010, IT
Dry extract (1.5-5:1), extraction solvent ethanol 60% m/m	For the relief of mental and physical symptoms of stress and overwork, such as fatigue, exhaustion, irritability and tension.	Film-coated tablet *Adults:* SD 200 mg DD 400 mg Do not use for more than 6 months. If the symptoms persist longer than 2 weeks	TUR, 5.6.2014, BE

Active substance	Indication	Pharmaceutical form	Regulatory Status
		during the use of the medicinal product or worsen, a doctor or a person qualified in medical heath care should be consulted.	
Dry extract (1.5-5:1), extraction solvent ethanol 60% m/m	THMP for the temporary relief of symptoms related to stress such as fatigue and weakness.	Film-coated tablet *Adults:* SD 200 mg DD 400 mg If the symptoms persist longer than 2 weeks during the use of the medicinal product or worsen, a doctor or a person qualified in medical heath care should be consulted.	TUR, 23.10.2014, BG
Dry extract (1.5-5:1), extraction solvent ethanol 60% m/m	THMP for the temporary relief of symptoms related to stress such as fatigue and weakness.	Film-coated tablet *Adults:* SD 200 mg DD 400 mg If the symptoms persist longer than 2 weeks during the use of the medicinal product or worsen, a doctor or a person qualified in medical heath care should be consulted.	TUR, 2015, CZ
Dry extract (1.5-5:1), extraction solvent ethanol 60% m/m	THMP for the temporary relief of symptoms related to stress such as fatigue and weakness.	Film-coated tablet *Adults:* SD 200 mg DD 400 mg If the symptoms persist longer than 2 weeks during the use of the medicinal product or worsen, a doctor or a person qualified in medical heath care should be consulted.	TUR, 2018, SK

Active substance	Indication	Pharmaceutical form	Regulatory Status
Dry extract (1.5-5:1), extraction solvent ethanol 60% m/m	THMP for the temporary relief of symptoms related to stress such as fatigue and weakness.	Film-coated tablet *Adults:* SD 200 mg DD 400 mg If the symptoms persist longer than 2 weeks during the use of the medicinal product or worsen, a doctor or a person qualified in medical heath care should be consulted.	TUR, 30.8.2016, HR
Dry extract (1.5-5:1), extraction solvent ethanol 60% m/m	THMP for the relief of temporary symptoms related to stress such as fatigue and weakness.	Film-coated tablet *Adults:* SD 200 mg DD 400 mg If the symptoms persist longer than 2 weeks during the use of the medicinal product or worsen, a doctor or a person qualified in medical heath care should be consulted.	TUR, 2008, AT
Dry extract (1.5-5:1), extraction solvent ethanol 60% m/m	THMP for the temporary relief of symptoms related to stress such as fatigue and weakness.	Film-coated tablet *Adults:* SD 200 mg DD 400 mg If the symptoms persist longer than 2 weeks during the use of the medicinal product or worsen, a doctor or a person qualified in medical heath care should be consulted.	TUR, 2009, NL
Dry extract of root and rhizome (2.5-5:1) first extraction solvent ethanol 70%, second extraction solvent water	THMP used as an adaptogen at decreased performance, such as fatigue and weakness.	Coated tablet Adults and adolescents: SD 144 mg DD 144-288 mg If the symptoms persist longer than 2 weeks during the use of the medicinal	Natural remedy (national legislation) 1987-2008, since 2008 registered as a THMP, SE

Active substance	Indication	Pharmaceutical form	Regulatory Status
		product or worsen, a doctor or a person qualified in medical heath care should be consulted.	
Dry extract (1.5-5:1), extraction solvent ethanol 60% m/m	THMP for the temporary relief of symptoms related to stress such as fatigue and weakness.	Film-coated tablet *Adults:* SD 200 mg DD 400 mg If the symptoms persist longer than 2 weeks during the use of the medicinal product or worsen, a doctor or a person qualified in medical heath care should be consulted.	TUR, 2010-2017, SE

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

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

Not applicable.

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

Not applicable.

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

Not applicable

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

Saratikov (1974) reports that in 1969, the Ministry of Health of the former USSR has recommended to allow the medical utilisation and industrial production of the liquid extract of the *Rhodiola*. In this paper, a herbal tea and a tincture prepared with ethanol 40% (or vodka) are mentioned as traditional herbal preparations. In 1975 *Rhodiola* fluid extract was accepted in the former USSR as a 'Temporary Pharmacopoeial Article' which allowed the large-scale industrial production of a liquid extract (DER 1:1, extraction solvent ethanol 40%). The products were in use also in those parts of the former USSR which now belong to the European Union (Estonia, Latvia, Lithuania), which was confirmed by the National Medicines Agency of Lithuania. However, there are no reports on a current medicinal use.

Table 2: Overview of historical data

Herbal preparation	Documented use / Traditional use	Posology, strength	Reference
Liquid extract, DER 1:1, extraction solvent ethanol 40%	Asthenia, fatigue, dystonia	Single dose 5-10 drops, 15-30 minutes before the meal; 2-3 times daily Duration of use: 10-20 days	Saratikov (1974)

2.3. Overall conclusions on medicinal use

The registrations in the EU member states were granted based on the traditional medicinal use of the herbal preparations listed in table 3.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Dry extract, DER 2.5-5:1, first extraction solvent ethanol 70% V/V, second extraction solvent water	Traditional herbal medicinal product used as an adaptogen at decreased performance, such as fatigue and weakness.	One tablet contains 144 mg dry extract. Dosage: 1 tablet 1-2 times daily.	Since 1987 in SE
Dry extract (1.5-5:1), extraction solvent ethanol 60% m/m (= 67.7% V/V)	THMP for the temporary relief of symptoms related to stress such as fatigue and weakness.	Film-coated tablet *Adults:* SD 200 mg DD 400 mg If the symptoms persist longer than 2 weeks during the use of the medicinal product or worsen, a doctor or a person qualified in medical heath care should be consulted.	Registrations based on the above-mentioned dry extract in several member states since 2008.

Clinical efficacy based on Article 10a of Directive 2001/83/EC (well-established use), is evaluated in chapter 4 'Clinical data'.

Based on information on the medicinal use, the requirements for traditional medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA of Directive 2001/83/EC, were considered fulfilled in the first version of the monograph for:

Dry extract (DER 1.5-5:1), extraction solvent ethanol 67-70% V/V. Posology for adults and elderly 144-200 mg 1-2 times daily.

Based on the traditional medicinal use and under considerations of indication of EU herbal monographs of other herbal substances, the indication has been slightly modified since the first version of the monograph as follows:

Traditional herbal medicinal product for the relief of symptoms of stress, such as fatigue and exhaustion. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

Pharmacological data of herbal preparations:

Anti-fatigue effects:

In vivo

Lee *et al.* (2009): An extract of *Rhodiola rosea* (no details on extraction solvent and DER, approximately 1.4% salidroside, 0.4% rosin, 0.4% rosarin, 1% rosavin) was tested on swimming-induced fatigue in rats. The supplementation (dosages from 5 to 125 mg per kg) in water for 2-4 weeks was evaluated in male Wistar rats with 90-minutes unloaded swimming exercise and 5% body weight loaded swimming up to fatigue. The authors report that the extract increased liver glycogen, SREBP-1, FAS, heat shock protein 70 expression, B-cell lymphoma 2/Bax protein ratio and oxygen content before swimming. *Rhodiola rosea* supplementation in water increased the swimming time in a dose-dependent manner and reduced swimming-enhanced serum BUN, GOT and GPT levels. The ratio of red and white muscle fibres was not altered after chronic *Rhodiola rosea* extract supplementation in water.

Abidov *et al.* (2003): The effects of oral treatment with an ethanolic extract (ethanol 40%) from *Rhodiola rosea* (50 mg per kg) and *Rhodiola crenulata* (50 mg per kg) roots on the duration of exhaustive swimming and ATP content in mitochondria of skeletal muscles in rats was investigated. According to the authors, the result showed that treatment with *Rhodiola rosea* extract prolonged the duration of exhaustive swimming by 24.6% in comparison with control rats and rats treated with *Rhodiola crenulata*. *Rhodiola rosea* extract activated the synthesis or resynthesis of ATP in mitochondria and stimulated reparative energy processes after intense exercise.

Stress-protective effects:

In vivo

Mattioli & Perfumi (2007): The aim of this work was to determine whether in rats a hydroalcoholic *Rhodiola rosea* extract (no details on the strength of the extraction solvent published) standardised in 3% rosavin and 1% salidroside reverses hypophagia induced by (1) physical stress due to 60 minutes immobilisation; (2) intracerebroventricular injection of corticotrophin-releasing factor (CRF, 0.2 µg/rat), the major mediator of stress responses in mammals; (3) intraperitoneal injection of Escherichia coli Lipopolysaccharide (LPS, 100 µg per kg); (4) intraperitoneal administration of

fluoxetine (FLU, 8 mg per kg). The effect of the same doses of the plant extract was also tested in freely-feeding and in 20 hours food-deprived rats. The extract was administered acutely by gavage to male Wistar rats 1 hour before the experiments. The authors conclude that the results show that at doses of 15 and 20 mg per kg the extract reversed the anorectic effects induced both by immobilisation and by intracerebroventricular CRF injection. Moreover, at the same doses, the extract failed to reduce the anorectic effect induced both by LPS and FLU and did not modify food intake in both freely-feeding and food-deprived rats. The authors interpret the results that *Rhodiola* extract is able selectively to attenuate stress-induced anorexia, providing functional evidence of claimed adaptogen and anti-stress properties of *Rhodiola rosea* L.

Zhu *et al.* (2003): The contents of glycogen, lactic acid and cholesterol in the liver of noise-stressed rats were analysed in order to investigate the alleviation of noise-stress-induced physiological damages by a decoction of the underground organs of *Rhodiola rosea*. More than 95 dB noise ranging from 2 to 4 kHz reduced the contents of these compounds in the liver of rats not injected with the extract but did not change the contents in the liver of rats treated with the extract. The results indicate that *Rhodiola* extract improved the ability for rats to resist noise stress.

Boon-Niermeijer *et al.* (2000): The authors examined whether *Rhodiola* extract SHR-5 (DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water) is able to exert a protective action against stress-induced death of embryos of the pond snail *Lymnaea stagnalis*, and whether a possible protective action by the extract can be explained by the induction of heat shock proteins. The extract was applied for a period of 20 hours to 3-day old larvae of the pond snail. Subsequently they were exposed to a high and toxic dose of different environmental stressors (heat shock: 43° C for 4 minutes, an oxidative stress condition (superoxide radicals induced by menadione 600 µM for 2 hours) and heavy metal-induced stress (copper 150 µM for 1 hour or cadmium 20 µM during 1 hour). The authors state that *Rhodiola* extract exerted a strong protective action against a lethal heat shock. It also protected against the negative effect of superoxide radicals as induced by menadione. With respect to the protective action against exposure to heavy metals a small protection was observed against intoxication with copper or cadmium. Although the degree to which resistance is enhanced appears to depend on the type of stressor applied, the results confirm in the opinion of the authors the definition of phyto-adaptogens as being universal enhancers of non-specific resistance against different kinds of stress conditions. The extract did not induce the synthesis of any of the heat shock proteins, nor did it modulate the normal heat shock induced synthesis of these stress proteins. Therefore it is concluded that it is unlikely that heat shock proteins play a major role in obtaining an enhanced state of resistance provided by *Rhodiola* extracts.

Panossian *et al.* (2007): Blood levels of several mediators were analysed in rabbits subjected to restraint stress. Beside other herbal preparations one group of rabbits received orally 1 mg per kg of the *Rhodiola* extract SHR-5 for seven consecutive days. The effect on the blood levels of the mediator substances were compared between animals receiving placebo and stress, animals receiving study medication without stress and animals receiving study-medications and stress. The stress was induced by immobilisation of the animals for 2 hours. In the placebo-group the levels of phosphorylated kinase (p-SAPK/p-JNK), nitric oxide, and cortisol were increased significantly. In animals treated with Rhodiola the levels of nitric oxide and cortisol remained unchanged.

Mattioli *et al.* (2009): The aim of this study was to determine whether chronic treatment with a hydroalcoholic *Rhodiola rosea* extract (no details on the strength of the extraction solvent published) containing 3% rosavin and 1% salidroside can prevent alterations induced in female rats following 6 weeks of a chronic mild stress (CMS) procedure. This was analysed through the behavioural and physiological parameters of consumption of 1% sucrose solution, locomotor and exploratory activities, body weight gain and oestrous cycle length. After the first 3 weeks of stress, the extract was administered daily by gavage at doses of 10, 15 and 20 mg per kg for the remaining 3 weeks. In

addition, fluoxetine (10 mg per kg orally), which has been shown to reverse CMS-induced disruptions, was used as the reference treatment. Rats subjected to the CMS procedure demonstrated decreased sucrose intake, reduced moving behaviour, minimised weight gain and dysregulation of their oestrous cycle. Treatment with the *Rhodiola* extract reverted all of these changes. The effects of the extract were comparable to those of fluoxetine. The authors are of the opinion that chronic administration of *Rhodiola* extract results in potent inhibition of the behavioural and physiological changes induced by chronic exposure to mild stressors.

Chen *et al.* (2008a, only abstract available): The aim of the study was to explore the effects of *Rhodiola rosea* on the body weight and the intake of sucrose and water in depressive rats induced by chronic mild stress. A total of 70 male Sprague Dawley (SD) rats were divided into seven groups, including normal control group (treated with 0.5% sodium carboxymethycellulose), untreated group, negative control group (treated with 0.5% sodium carboxymethycellulose), positive control group (treated with fluoxetine), low-, medium- and high-dose *Rhodiola rosea* group (treated with 1.5, 3, 6 g per kg *Rhodiola rosea* respectively, no details on the type of herbal preparation available). Except for rats in normal control group, the other sixty rats endured chronic stress for 4 weeks to establish the depression model. After that, rats were administered *Rhodiola rosea* for 3 weeks. After the termination of the stress regime, compared with the normal control group, the body weight and 1% sucrose intake in depressive rats were decreased. After 3-week *Rhodiola rosea* treatment, the body weight and 1% sucrose intake increased in rats of the low-dose *Rhodiola rosea* group and recovered to the level of the normal control group.

Cifani *et al.* (2010): Binge eating (BE) for highly palatable food (HPF) was evoked in female rats by three 8-day cycles of food restriction/re-feeding (for 4 days 66% of the usual chow intake; for 4 days food ad libitum) and acute stress on the test day (day 25). *Rhodiola rosea* dry extract (3% rosavin, 3.12% salidroside no details on extraction solvent) or its active principles were given by gavage 1 hour before access to HPF. Only rats exposed to both food restrictions and stress exhibited BE in the first 15-60 minutes after the stressful procedure. The authors report that the *Rhodiola rosea* extract 10 mg per kg reduced and 20 mg per kg abolished the BE episode. *Rhodiola rosea* extract 20 mg per kg abolished also stress-induced increase in serum corticosterone levels. The *Rhodiola rosea* active principle salidroside, but not rosavin, at doses present in the extract, dose-dependently reduced or abolished BE for the period in which it was elicited.

Dinel *et al*. (2019) administered an extract prepared from frozen fresh *Rhodiola rosea* roots using ethanol 20% - 70% V/V (DER 17:1, content of salidroside 1.02 mg/ml) to Balb/c mice (5 g per kg for 2 weeks). After the treatment the mice were submitted a mild stress protocol (open-field test, elevated maze). The corticosterone levels were lower in treated mice compared to the control group and comparable to treated but not stressed mice. In the excised hippocampus and prefrontal cortex an increased expression of stress-responsive genes could be found.

Kumar *et al*. (2018) administered orally a *Rhodiola rosea* dry extract (extraction solvent ethanol 60% m/m, DER 1.5-5:1) to adult Charles foster albino rats in doses of 50, 150 and 450 mg per kg bw once daily for 14 days. During this period the rats were subjected to electrical foot shocks to produce a state of chronic stress. The treatment resulted in a dose-dependent normalisation of brain nor-epinephrin, 5-HT and dopamine. The authors report that in the higher doses the plasma corticosterone levels were lower compared to vehicle-treated animals.

In vitro

Borgonetti *et al.* (2020) investigated the modulatory effect of a *Rhodiola rosea* extract (dry extract (1.5-5:1), extraction solvent ethanol 60% m/m) on neuroinflammatory parameters in an *in vitro* model of corticotropin releasing hormone-stimulated BV2 microglial cells. The extract counteracted the

neuroinflammatory effect of corticotropin releasing hormone by inhibiting NF-κB nuclear translocation. The authors interpret this result as an intracellular mechanism related to anti-stress activity.

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

Herbal preparation tested	**Posology**	**Experimental model**	**Reference**	**Main non-clinical conclusions**
Extract containing approximately 1.4% salidroside, 0.4% rosin, 0.4% rosarin, 1% rosavin (no further information)	5-125 mg per kg orally in water	Male Wistar rats, 90-minutes unloaded swimming exercise and 5% body weight loaded swimming up to fatigue	Lee *et al.* (2009)	Dose dependent increase in swimming time
Extract with ethanol 40% V/V, 3.02% rosavines, 0.89% salidroside (no further information)	50 mg per kg by gavage	Rats, exhaustive swimming exercise	Abidov *et al.* (2003)	Prolonged duration of exhaustive swimming
Hydroalcoholic extract containing 3% total rosavines and1% salidroside (no further information)	10, 15 and 20 mg per kg by intragastric administration	Male Wistar rats Induced hypohphagia	Mattioli & Perfumi (2007)	Attenuation of stress-induced anorexia
SHR-5 (DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water	1 mg per kg, orally	Rabbits Blood levels of mediator substances with and without stress induction	Panossian *et al.* (2007)	The levels of NO and cortisol remained unchanged in treated animals
Hydroalcoholic extract containing 3% total rosavines and1% salidroside (no further information)	10, 15 and 20 mg per kg by gavage	Female rats following 6 weeks chronic mild stress	Mattioli *et al.* (2009)	Rhodiola supplementation reverted the decreased sucrose intake, reduced moving behaviour, minimized weight gain and dysregulation of the oestrus cycle towards normal values
Dry extract (extraction solvent ethanol 60% m/m, DER 1.5-5:1)	50, 150 and 450 mg per kg , orally	Charles foster albino rats Chronic stress by electrical foot shocks	Kumar *et al*. (2018)	Higher doses lowered the plasma corticosterone levels compared to vehicle-treated animals

3.1.2. Secondary pharmacodynamics

Oxidative stress, antioxidative effects:

In vitro

Battistelli *et al.* (2005): An aqueous extract (100 mg herbal substance in 2.4 ml water, 3-fold extraction) was applied *in vitro* to human erythrocytes which were exposed to hypochlorous acid (HOCl)-oxidative stress. The evaluation of the antioxidant capacity of the *Rhodiola* extract has been carried out by means of scanning electron microscopy and of haemolytic behaviour in the presence of increasing doses of the aqueous extract in different experimental environments (co-incubation and subsequent incubations). The authors report that the results obtained show protection of the extract in presence of the oxidative agent.

De Sanctis *et al.* (2004): An aqueous extract (12 mg dried herbal substance in 2.4 ml final volume) was tested for its ability to counteract some of the main damages induced by HOCl to human erythrocytes. Ascorbic acid was used as a reference substance because of its physiological HOCl-scavenging ability. According to the authors, the extract protected in a dose-dependent manner human red blood cells from glutathione depletion, glyceraldehyde-3-phosphate dehydrogenase inactivation and haemolysis induced by the oxidant. It was demonstrated that the extract acts from the inside of the erythrocyte suggesting a probable involving of cell components.

Calcabrini *et al.* (2010): The authors investigated the protection afforded by an aqueous extract (DER 1:1) to reduce glutathione levels, glyceraldehyde-3-phosphate dehydrogenase activity, and thiobarbituric acid reactive substances levels in cultured human keratinocytes (NCTC 2544) exposed to different oxidative insults (Fe(II)/ascorbate, Fe(II)/H(2)O(2), and tert-butyl-hydroperoxide) as well as the influence of the extract on the production of intracellular reactive oxygen species and on the activity of antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase). It was reported that the extract was able to increase in a time- and dose-dependent manner the activity of the trans-plasma membrane oxido reductase activity as an indirect evaluation of the intracellular redox status. Keratinocytes of the type NCTC 2544 are able to better counteract several oxidative insults if incubated with a *Rhodiola rosea* aqueous extract.

Chen *et al.* (2008a, only abstract available): This study investigated the antioxidant potential of 3 adaptogen extracts, *Rhodiola rosea* (golden root), *Eleutherococcus senticosus* (Siberian ginseng) and *Emblica officinalis* (Indian gooseberry, Amla). The authors state that the results of this study showed that *Rhodiola rosea* had the highest potential for singlet oxygen scavenging, hydrogen peroxide scavenging, ferric reducing, ferrous chelating and protein thiol protection than either of the other two extracts. In addition, the polyphenol content in the three adaptogen extracts followed the order: *Rhodiola rosea*, *Eleutherococcus officinalis and Eleutherococcus senticosus*. The data suggests that the antioxidant potential of the three adaptogen extracts was proportional to their respective polyphenol content.

Palumbo *et al*. (2012) found that the antioxidant activity of *Rhodiola rosea* (dry extract, extraction solvent ethanol 80%, DER 10:1) may be caused by a stabilisation of the Ca^{2+} homeostasis.

Schriner *et al.* (2009a): A *Rhodiola rosea* extract (no details published) could protect cultured cells against ultraviolet light, paraquat, and H_2O_2. However, it did not alter the levels of the major antioxidant defences, nor did it markedly activate the antioxidant response element or modulate heme-oxygenase-1 expression levels at relevant concentrations. In addition, *Rhodiola rosea* extract was not able to significantly degrade H_2O_2 *in vitro*. These results suggest that in human cultured cells *Rhodiola rosea* does not act as an antioxidant and that its mode of action cannot be sufficiently explained through a pro-oxidant hormetic mechanism.

Life-span increasing effects:

In vivo

Schriner *et al.* (2009, only abstract available): The extract SHR-5 (DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water) could extend both mean (24% in both sexes) and maximum (16% in males and 31% in females) life span in Drosophila melanogaster when compared to controls. It lowered mitochondrial superoxide levels and afforded elevated protection against the superoxide generator paraquat in both sexes. The extract did not alter the activities of the major antioxidant enzymes, the superoxide dismutase or catalase, nor did it afford protection against H_2O_2 or soluble iron.

Jafari *et al.* (2007): Using the fruit fly, Drosophila melanogaster, the effects of *Rhodiola* extract (no details published) on life-span was investigated. *Rhodiola* supplied every other day at 30 mg/ml increased the lifespan of Drosophila melanogaster. When comparing the distribution of deaths between *Rhodiola*-supplemented and control flies, *Rhodiola*-fed flies exhibited decelerated aging. The authors conclude that although the observed extension in lifespan was associated with statistically insignificant reductions in fecundity, correcting for a possible dietary restriction effect still did not eliminate the difference between supplemented and control flies, nor does the effect of *Rhodiola* depend on dietary manipulation, suggesting that *Rhodiola* is not a mere dietary restriction mimetic.

Wiegant *et al.* (2009): Extracts of *Rhodiola* (SHR-5, DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water) and of *Eleutherococcus* increased the mean lifespan of the nematode C. elegans in a dose-dependent way. In at least four independent experiments, 250 µg/ml *Eleutherococcus* and 10-25 µg/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 µg/ml *Eleutherococcus* and 250 µg/ml *Rhodiola*) 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 hours) 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 UV stress, be it less efficiently. Both extracts induced the translocation of the DAF-16 transcription factor from the cytoplasm into the nucleus, suggesting a reprogramming of transcriptional activities favouring the synthesis of proteins involved in stress resistance (such as the chaperone HSP-16) and longevity.

Effects on nervous system

In vivo

Qu *et al.* (2009): The authors investigated the pre-treatment effects of *Rhodiola rosea* extract (no details on extraction solvent published) on cognitive dysfunction, oxidative stress in hippocampus and hippocampal neuron injury in a rat model of Alzheimer's disease. Male Sprague-Dawley rats were pre-treated with *Rhodiola rosea* extract at doses of 1.5, 3, and 6 g per kg for 3 weeks by gavage twice daily, followed by bilateral intracerebroventricular injection with streptozotocin (1.5 mg per kg) on day 1 and 3. Behavioural alterations were monitored after 2 weeks from the lesion using Morris water maze task. Three weeks after the lesion, the rats were sacrificed for measuring the malondialdehyde (MDA), glutathione reductase (GR) and reduced glutathione (GSH) levels in hippocampus and histopathology of hippocampal neurons. The authors report that the MDA level was increased while the GR and GSH levels were decreased with striking impairments in spatial learning and memory and severe damage to hippocampal neurons in the model rat induced by intracerebroventricular injection of streptozotocin. These abnormalities were improved by pre-treatment with *Rhodiola rosea* extract (3 g per kg).

Perfumi & Mattioli (2007): The purpose of the present study was to investigate the effects produced by a single oral administration of a *Rhodiola rosea* hydroalcoholic extract (containing 3% rosavin and 1%

salidroside, no information on the extraction solvent published) on the central nervous system in mice. The extract was tested on antidepressant, adaptogenic, anxiolytic, nociceptive and locomotor activities at doses of 10, 15 and 20 mg per kg, using predictive behavioural tests and animal models. The authors state that the results show that this *Rhodiola rosea* extract, but not dose-dependently, induced antidepressant-like, adaptogenic, anxiolytic-like and stimulating effects in mice.

Chen *et al.* (2009): The purpose of this study was to investigate the effects of *Rhodiola rosea* extract (ethanol 70%) on the serotonin (5-HT) level, cell proliferation and quantity of neurons in the cerebral hippocampus of depressive rats induced by Chronic Mild Stress. After 3 weeks of oral administration of 1.5 g up to 6 g per kg per day 5-HT level had recovered to normal status. In the low dose group the extract induced neural stem cell proliferation in the hippocampus to return to normal level, repairing the injured neurons in the hippocampus.

Qin *et al.* (2008, only abstract available): The purpose of this study was to investigate the effects of *Rhodiola rosea* (no details on the type of the herbal preparation available) on the level of 5-HT, cell proliferation and differentiation, and number of neurons in the cerebral hippocampus of rats with depression induced by chronic mild stress. After 3 weeks of administration of the preparation all measured parameters like 5-HT content, number of bromodeoxyuridine positive cells, percentage of bromodeoxyuridine and beta-tubulin III double labelled cells and number of neurons in the cerebral hippocampus returned to normal level.

Panossian *et al.* (2008): The antidepressant-like activity of an extract of the roots of *Rhodiola rosea* (DER 2.5-5:1, no information on the extraction solvent, containing 2.7% rhodioloside, 6% rosavin, 0.8% tyrosol), its combination with piperine, isolated constituents from *Rhodiola*, such as rhodioloside, rosavin, rosin, rosarin, tyrosol, cinnamic alcohol, cinnamaldehyde and cinnamic acid has been assessed in laboratory animals through application of the Porsolt behavioural despair assay. The orally administered extract reduced in dosages of 10, 20 and 50 mg per kg dose-dependently the immobility time more strongly compared to *Hypericum* extract LI160 (20 mg per kg), amitriptyline (3 mg per kg) or imipramine (30 mg per kg). The combination with piperine was also active in a similar degree, but no dose-dependency was detectable. The authors report that rhodioloside and tyrosol contributed considerably to this effect. A fixed combination of rhodioloside, rosavin, rosarin and rosin was more active than any of the individual components alone.

Mattioli & Perfumi (2011): The authors investigated the effects of a *Rhodiola rosea* hydroalcoholic extract (no details on extraction solvent published, 3% total rosavins, 1% salidroside) on the prevention of the development of nicotine dependence and for the reduction of abstinence suffering following nicotine cessation in mice. Dependence was induced in mice by subcutaneous injections of nicotine (2 mg per kg, 4 times daily) for 8 days. Spontaneous abstinence syndrome was evaluated 20 hours after the last nicotine administration, by analysis of withdrawal signs, as affective (anxiety-like behaviour) and physical (somatic signs and locomotor activity). The extract was administered orally during nicotine treatment (10, 15 and 20 mg per kg) or during nicotine withdrawal (20 mg per kg). Both affective and somatic signs (head shaking, paw tremors, body tremors, ptosis, jumping, piloerection and chewing) induced by nicotine withdrawal were abolished by administration of the extract in a dose-dependent fashion, during both nicotine exposure and nicotine cessation.

Mattioli & Perfumi (2011a): The same extract, as in Mattioli & Perfumi (2011) was investigated for effects on acquisition and expression of morphine tolerance and dependence in mice. Therefore animals were injected with repeated administration of morphine (10 mg per kg, subcutaneous) twice daily for 5 or 6 days, in order to make them tolerant or dependent. The extract (0, 10, 15 and 20 mg per kg) was administered by the intragastric route 60 minutes prior to each morphine injection (for acquisition) or prior the last injection of morphine or naloxone on test day (for tolerance or dependence expression, respectively). Morphine tolerance was evaluated by testing its analgesic effect

in the tail flick test at the 1st and 5th days. Morphine dependence was evaluated by counting the number of withdrawal signs (jumping, rearing, forepaw tremor, teeth chatter) after naloxone injection (5 mg per kg; intraperitoneal) on the test day (day 6). The authors state that the extract reduced the expression of morphine tolerance, while it was ineffective in modulating its acquisition. Conversely, *Rhodiola rosea* extract dose-dependently attenuated both development and expression of morphine dependence after chronic or acute administration.

Montiel-Ruiz *et al*. (2012) administered orally a dry extract of *Rhodiola rosea* (extraction solvent ethanol 70% V/V, containing 2.5% salidroside and 2.7% rosavin) to mice in one single dose of 10-316 mg per kg bw. Rhodiola induced reduction in the exploratory behaviour of the animals, but no change in the sedative-hypnotic and anticonvulsant response compared to vehicle. In doses up to 5000 mg per kg bw no toxic effects nor changes in the behavioural pattern were observed.

Cayer *et al*. (2013) administered an ethanolic extract of *Rhodiola rosea* (ethanol 90%, extract yield 7%) to Sprague-Dawley rats in doses of 8 mg per kg, 25 mg per kg and 75 mg per kg bw. The extract exhibited dose-dependently anxiolytic activity in the elevated plus maze and conditioned emotional response tests. In an *in vitro* $GABA_A$-benzodiazepine receptor-binding assay only low activity was found suggesting that other pathways are primarily involved in the anxiolytic effects.

Mannucci *et al*. (2012) investigated a *Rhodiola rosea* dry extract (extraction solvent ethanol 60% m/m, DER 1.5-5:1) in nicotine dependent rats in doses of 5-40 mg per kg bw. The analysis of behavioural parameters as well as diencephalic serotonin metabolism and serotonin receptor-1A expression after withdrawal of nicotine suggest an involvement of serotonine in rats treated with Rhodiola.

In vitro

Van Diermen *et al.* (2009): In order to investigate the influence of *Rhodiola rosea* roots on mood disorders, three extracts were tested against monoamine oxidases (MAOs A and B) in a microtiter plate bioassay. Twelve compounds were then isolated by bioassay-guided fractionation using chromatographic methods. The methanol and water extracts exhibited respectively inhibitions of 92.5% and 84.3% on MAO A and 81.8% and 88.9% on MAO B, at a concentration of 100 µg/ml. The most active compound (rosiridin) presented an inhibition over 80% on MAO B at a concentration of $10^{(-5)}$ M (pIC_{50}=5.38+/-0.05).

Asea *et al*. (2013) investigated several herbal preparations on their ability to induce the release of heat shock protein 70 (Hsp 72) which is mediated by neuropeptide Y (NPY) in neuroblastoma cells. Only extracts of putative adaptogens (among them the *Rhodiola rosea* extract SHR-5 (DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water) stimulated both Hsp 72 and NPY. The results were confirmed in primary human neurons. The authors conclude that Hsp 72 and NPY may be used as molecular biomarkers for adaptogenic activity.

Shen *et al*. (2013) could not find neuroprotective effects of an extract prepared with ethanol 60% in cultured mouse cortical neurons, although a significant antioxidant capacity in non-cellular assays was seen. In contrast, some neurotoxicity was found at concentrations of 100 µg/ml.

Cardio protective effects, effects on the vascular system:

In vivo

Maslov *et al.* (2009, only abstract available): A course of treatment (16 mg per kg orally during 5 days) by *Aralia mandshurica* or *Rhodiola rosea* extracts (no details available) reduced the incidence of ischemic and reperfusion ventricular arrhythmias during 10 minutes ischemia and 10 minutes reperfusion in rats. Chronic treatment by *Aralia*, *Rhodiola*, and *Eleutherococcus* elevated the ventricular fibrillation threshold in rats with postinfarction cardiosclerosis.

Li *et al.* (2005, only abstract available): On the basis of successful establishment of myocardial infarction rat model, the experimental animals were divided into the model group, the *Rhodiola* group (no details on the type of the herbal preparation and on posology available), the positive control group and the sham-operated group, they were sacrificed after 6 weeks feeding. The authors report that the expressions of Flt-1 and angiopoietin receptor (Tie-2) in myocardial tissue were increased in the *Rhodiola* treated group after treatment, showing significant difference as compared with those in the positive control group and the model group ($p<0.05$). The expression of the growth factor KDR in myocardium after *Rhodiola* intervention was higher than that in the sham-operated and nonintervened group ($p<0.05$), but insignificantly different to that in the positive control group and model group. Therefore it was concluded that *Rhodiola* could improve angiogenesis to ameliorate myocardial ischemia by regulating the expression of Flt-1 and Tie-2 in ischemic myocardium.

Shen *et al.* (2008, only abstract available): Thirty male New Zealand rabbits were randomly divided into three groups equally, i.e. the control group (A) fed with common diet and treated with distilled water, the high fat diet group (B) and the *Rhodiola* group (C, no details on the type of the herbal preparation and on dosage available) fed with diet containing 1.5% cholesterol and treated respectively with distilled water and *Rhodiola* (1 ml per kg per day), all the treatments were administered via gastrogavage once daily for 9 successive weeks. Levels of blood lipids in various groups was determined and compared at the end of the experiment. Meanwhile, the tissue sample of aorta was taken for observation through HE and Sudan red staining, for detecting the CD34 positive response intensity by immunohistochemical staining and the vascular endothelial cell growth factor VEGF expression by Real-time fluorescent quantitative PCR and Western blot. The determination of blood lipids showed that in Group C, TC was 42.01 +/- 1.99 mmol/L, TG 4.83 +/- 0.75 mmol/L and LDL-C 38.40 +/- 0.74 mmol/L, all lower than those in Group B (70.74 +/- 2.66 mmol/L, 8.75 +/- 0.78 mmol/L and 51.05 +/- 0.34 mmol/L, respectively), showing statistical difference between groups ($p<0.05$). The intima/media tunica thickness ratio and the CD34 positive area of plaque in Group C were all lower than those in Group B (0.35 +/- 0.03 vs 0.43 +/- 0.03 and 29.12 +/- 2.56% vs 39.28 +/- 3.48%, $p<0.05$). Besides, the VEGF expression in atherosclerotic plaque was also lower in Group C than that in Group B.

Maslov & Lishmanov (2007, only abstract available): The chronic administration of *Rhodiola rosea* extract (no details available) in a single daily dose of 1 ml per kg (p.o.) during 8 days increased the resistance of myocardium with respect to the cardiotoxic action of isoproterenol and the arrhythmogenic action of epinephrine in rats. Pre-treatment with the extract prevented the stressor cardiac damages, as measured by 99mTc-pyrophosphate accumulation in the heart. The cardioprotective action of RRE was highest after 5-day administration. The antiarrhythmic effect of the adaptogen was at a maximum after 8-day administration. It was found that p-tyrosol also exhibited antiarrhythmic and cardioprotective properties. Pre-treatment with the extract decreased the infarction size/risk area ratio during the coronary artery occlusion and reperfusion *in vivo*. The chronic administration of the extract increased the tolerance of the isolated perfused rat heart to the pathogenic action of global ischemia and reperfusion. Pre-treatment not only prevented the occurrence of arrhythmias, but also abolished cardiac electrical instability in rats with postinfarction cardiac sclerosis. It has been found that the chronic administration of the extract (1 ml per kg, p.o., over 8 days) increased the level beta-endorphin in rat blood plasma and the content of leu-enkephalin in myocardial tissue. Naloxone (2 mg per kg) abolished the cardioprotective and antiarrhythmic effect of the extract.

Anti-inflammatory effects:

In vivo

Pooja *et al.* (2009): The present study was undertaken to evaluate the anti-inflammatory effects of a liquid extract of *Rhodiola rosea* underground organs (extraction solvent ethanol 40%). The anti-inflammatory activity was determined through carrageenan-induced paw oedema, formaldehyde-induced arthritis and nystatin-induced paw oedema in rat model. The liquid extract exhibited inhibitory effect against acute and subacute inflammation at a dose of 250 mg per kg body weight. Inhibition of nystatin-induced oedema was also observed in a dose-dependent manner. The extract showed varying inhibitory activities against enzymes related to inflammation depending on the concentrations. A potent inhibition was observed against Cox-2 and phospholipase A_2. Inhibition of nystatin induced oedema and phospholipase A2 suggested that membrane stabilisation could be the most probable mechanism of action of the extract in anti-inflammation.

Lee *et al*. (2013) investigated a *Rhodiola rosea* extract (extraction solvent methanol, DER 1.4:1) as well as the isolated constituents rosin, rosarian and salidroside. The LPS-induced expression of iNOS and cytokines in murine microglial BV2 cells was suppressed in a dose-dependent manner. The expression of proinflammatory factors in the prefrontal cortex of the brain in mice was suppressed when the extract was administered orally in a dose of 500 mg per kg bw. The L-glutamate induced neurotoxicity was suppressed in neuronal cells by rosin but not by rosarin.

Effects on metabolism:

In vivo

Kim *et al.* (2006): This study was designed to examine the effects of *Cinnamomum cassia* and *Rhodiola rosea* extracts (dry extract DER 10:1, extraction solvent ethanol 85%) on blood glucose, lipid peroxidation, the level of reduced glutathione and its related enzymes (glutathione reductase, glutathione S-transferase), and the activity of the antioxidant enzymes (catalase, superoxide dismutase and glutathione peroxidase) in the liver of db/db mice. Diabetic C57BL/Ks db/db mice were used as experimental models. Mice were divided into control (n=10), *Cinnamomi cassiae* (200 mg per kg per day, n=10), and *Rhodiola rosea* (200 mg per kg per day, n=10) treated groups for 12 weeks of oral treatment. The authors state that both extracts decreased blood glucose, increased levels of reduced glutathione and the activities of glutathione reductase, glutathione S-transferase, glutathione peroxidase, catalase and superoxide dismutase in the liver. Extract treatment also decreased lipid peroxidation.

Effects on the endocrinous system:

In vitro

Kwon *et al.* (2006): Two species of the genus *Rhodiola* (*Rhodiola crenulata* and *Rhodiola rosea*) were investigated for the inhibition of α-amylase, α-glucosidase and angiotensin converting enzyme (ACE) inhibitory activity. Water extracts of *Rhodiola crenulata* had the highest alpha-amylase inhibitory activity (IC_{50}, 98.1 µg total phenolic/ml) followed by ethanol extract of *Rhodiola crenulata* (IC_{50}, 120.9 µg total phenolic/ml) and ethanol extract (ethanol 12%) of *Rhodiola rosea* (IC_{50}, 173.4 µg total phenolic/ml). Ethanol extract of *Rhodiola rosea* (IC_{50}, 44.7 µg total phenolic/ml), water extract (macerate DER 1:10) of *Rhodiola rosea* (IC_{50}, 52.3 µg total phenolic/ml), water extract of *Rhodiola crenulata* (IC_{50}, 60.3 µg total phenolic/ml) and ethanol extract of *Rhodiola crenulata* (IC_{50}, 60.2 µg total phenolic/ml) also showed significant α-glucosidase inhibitory activity. The α-glucosidase inhibitory activity of the extracts was compared to standard tyrosol, which was significantly detected in the extracts using HPLC. Tyrosol had strong α-glucosidase inhibitory activity (IC_{50}, 70.8 µg total phenolic/ml) but did not have any inhibitory effect on the α-amylase activity. Results suggested that α-glucosidase inhibitory activities of both *Rhodiola* extracts correlated to the phenolic content, antioxidant activity and phenolic profile of the extracts. The ability of the above *Rhodiola* extracts to

inhibit rabbit lung angiotensin I-converting enzyme (ACE) was investigated. The ethanol extracts of *Rhodiola rosea* had the highest ACE inhibitory activity (38.5%) followed by water extract of *Rhodiola rosea* (36.2%) and *Rhodiola crenulata* (15.4%).

Effects on hepatic tissue:

Ouyang *et al.* (2010, only abstract available): This study aimed to investigate whether salidroside can induce differentiation of rat mesenchymal stem cells (rMSCs) towards hepatocytes *in vitro* and the mechanism of hepatic differentiation of rMSCs. rMSCs were subject to hepatic differentiation. One, two and three weeks later, the expression of α-fetoprotein (AFP) and albumin (ALB), cytochrome P450 (CYP450)-dependent activity and inducibility, cellular uptake of low-density lipoprotein (LDL) and urea synthesis were assessed and the hepatic differentiation of rMSCs was evaluated. In order to unravel the mechanism of hepatic differentiation of rMSCs *in vitro*, inhibitors of extracellular regulated kinase1/2 (ERK1/2), phosphatidylinositol 3-kinase (PI3K) and p38 were applied. When the process of hepatic differentiation was completed, special proteins of hepatic differentiation were detected and blocking of inhibitors was evaluated. Salidroside significantly induced the differentiation of rMSCs towards hepatocytes. Differentiated rMSCs have typical functional hepatic characteristics. The results also showed that the ERK1/2 and PI3K signalling pathways play important roles in the regulatory effects of salidroside on hepatic differentiation of rMSCs and are involved in cell fate determinations, while the p38 signalling pathway does not.

Wu *et al.* (2009a, only abstract available): The aim was to investigate the protective effect of salidroside on D - galactosamine/lipopolysaccharide-induced fulminant hepatic failure. Hepatotoxicity was induced by an intraperitoneal injection of D-galactosamine (700 mg per kg) and lipopolysaccharide (10 μg per kg); salidroside (20, 50 and 100 mg per kg) was administered intraperitoneally 1 hour before induction of hepatotoxicity. Liver injury was assessed biochemically and histologically. Salidroside attenuated the induced acute increase in serum aspartate aminotransferase and alanine aminotransferase activities, and levels of TNF-α levels and serum nitric oxide. It restored depleted hepatic glutathione, superoxide dismutase, catalase and glutathione peroxidase activities, decreased malondialdehyde levels and considerably reduced histopathological changes. Histopathological, immunohistochemical and Western blot analyses also demonstrated that salidroside could reduce the appearance of necrotic regions and expression of caspase-3 and hypoxia-inducible factor-1α in liver tissue. The authors conclude that salidroside protected liver tissue from the oxidative stress elicited by D-galactosamine and lipopolysaccharide. The hepatoprotective mechanism of salidroside appears to be related to antioxidant activity and inhibition of hypoxia-inducible factor-1 α.

Wu *et al.* (2008): The protective effect of salidroside was investigated in the acetaminophen (APAP)-induced hepatic toxicity mouse model in comparison to N-acetylcysteine (NAC). Drug-induced hepatotoxicity was induced by an intraperitoneal injection of 300 mg per kg (sub-lethal dose) of APAP. Salidroside was given orally to mice at a dose of 50 or 100 mg per kg 2 hours before the APAP administration in parallel with NAC. Mice were sacrificed 12 hours after the APAP injection to determine aspartate aminotransferase (AST), alanine aminotransferase (ALT), and TNF-α levels in serum and glutathione (GSH) depletion, malondialdehyde (MDA) accumulation, and caspase-3 expression in liver tissues. Salidroside protected APAP-induced hepatotoxicity, as salidroside improved mouse survival rates better than NAC against a lethal dose of APAP and blocked not only APAP-induced increases of AST, ALT, and TNF- α but also APAP-induced GSH depletion and MDA accumulation. The authors report that histopathological and immunohistochemical analyses also demonstrated that salidroside could reduce the appearance of necrosis regions as well as caspase-3 and hypoxia inducible factor-1 α expression in liver tissue. The results indicated that salidroside protected liver tissue from the APAP-induced oxidative damage via preventing or alleviating intracellular GSH depletion and oxidation damage.

Effects on cancer cells:

Majewska *et al.* (2006): It has been found that the extract of *Rhodiola rosea* rhizomes (extraction solvent ethanol 96%) inhibits division of HL-60 cells, which is preceded by an accumulation of cells at the prophase stage. This leads to induction of apoptosis and necrosis in HL-60 cells, and to marked reduction of their survival. The cells enter apoptosis from phase G2/M of the cell cycle. After treatment with the extract, no chromosome aberrations or micronuclei were observed, which indicates the mild action of the extract.

Hu *et al.* (2010): To investigate the cytotoxic effects of salidroside on breast cancer cells and in order to reveal possible ER-related differences in response to salidroside, MDA-MB-231 cells and MCF-7 cells (oestrogen receptor-positive) were used as models to study possible molecular mechanisms. The effects of salidroside on cell growth characteristics, such as proliferation, cell cycle duration, and apoptosis, and on the expression of apoptosis-related molecules were evaluated. The results demonstrated that salidroside in concentration between 5μM and 80 μm dose-dependently induces cell-cycle arrest and apoptosis in human breast cancer cells.

Hu *et al*. (2010a): The present study focused on evaluating the effects of salidroside on the proliferation of various human cancer cell lines derived from different tissues, and further investigating its possible molecular mechanisms. Cell viability assay and [(3)H] thymidine incorporation were used to evaluate the cytotoxic effects of salidroside on cancer cell lines, and flow cytometry analysed the change of cell cycle distribution induced by salidroside. Western immunoblotting further studied the expression changes of cyclins (cyclin D1 and cyclin B1), cyclin-dependent kinases (CDK4 and Cdc2), and cyclin-dependent kinase inhibitors (p21(Cip1) and p27(Kip1)). The results showed that salidroside in concentration between 1 μg/ml and 32 μg/ml dose-dependently inhibited the growth of various human cancer cell lines in concentration- and time-dependent manners, and the sensitivity to salidroside was different in those cancer cell lines. Salidroside could cause G1-phase or G2-phase arrest in different cancer cell lines, meanwhile, salidroside resulted in a decrease of CDK4, cyclin D1, cyclin B1 and Cdc2, and upregulated the levels of p27(Kip1) and p21(Cip1). The authors conclude that salidroside could inhibit the growth of cancer cells by modulating CDK4-cyclin D1 pathway for G1-phase arrest and/or modulating the Cdc2-cyclin B1 pathway for G2-phase arrest.

Anti-bacterial activity:

Ming *et al*. (2005): Bioactivity-guided fractionation of a 95% ethanol extract from the stems of *Rhodiola rosea* led to the isolation of five compounds: gossypetin-7-O-L-rhamnopyranoside (1), rhodioflavonoside (2), gallic acid (3), trans-p-hydroxycinnamic acid (4) and p-tyrosol (5). Compounds 1 and 2 were evaluated for their antibacterial and antiprostate cancer cell activities. Compounds 1 and 2 exhibited activity against Staphylococcus aureus with minimum inhibitory concentrations of 50 μg/ml and 100 μg/ml, respectively. Cytotoxicity studies of 1 and 2 also displayed activity against the prostate cancer cell line with IC50 values of 50 μg/ml and 80 μg/ml, respectively.

Other effects:

Yin *et al*. (2009): This study aimed to investigate the inhibitory effect of salidroside on high glucose-induced mesangial cell proliferation and its possible mechanism. Salidroside (in concentrations from 1 to approximately 100 μM) dose dependently inhibited high glucose-induced mesangial cell early proliferation. Exposure of mesangial cells to high glucose for 24 hours significantly induced ROS accumulation, ERK1/2 phosphorylation, and p27 (Kip1) expression, and these changes were dramatically inhibited by salidroside in a dose-dependent manner. High glucose-promoted TGF- β1 secretion was also attenuated by treatment of mesangial cells with salidroside.

Wang *et al*. (2009a): The aim of this study was to investigate the antiviral effects of salidroside. The antiviral effects of salidroside against coxsackievirus B3 (CVB3) were determined *in vitro* and *in vivo*.

The effect of salidroside on the mRNA expression of some important cytokines was measured in hearts of infected BALB/c mice by RT-PCR. Salidroside exhibited obvious antiviral effects both in *in vitro* concentrations of 80 and 120 mg/l) and *in vivo* (concentrations between 20 and 80 mg per kg body weight) experiments. Salidroside was found to modulate the mRNA expression of interferon-gamma (IFN-gamma), interleukin-10 (IL-10), tumour necrosis factor-alpha (TNF-α), and interleukin-2 (IL-2).

Pharmacological data regarding isolated constituents:

Oxidative stress, antioxidative effects:

In vivo

Huang *et al*. (2009, only abstract available): Wistar rats received 5, 25, 125 mg of a Rhodiola extract per day for 4 weeks. Salidroside, rosin, rosavin and rosarin scavenged O2(-)*, H_2O_2, and HOCl activity in a dose-dependent manner. The 90 minutes swimming exercise increased the O2(-)* production in the order: liver > skeletal muscle > blood, indicating that liver is the most sensitive target organ. The level of plasma malonedialdehyde, a lipid peroxidation product, was also increased after exercise. Treatment of 4 weeks of *Rhodiola rosea* extracts significantly inhibited swimming exercise-enhanced O2(-)* production in the blood, liver and skeletal muscle and plasma malonedialdehyde concentration. The expression of Mn-superoxide dismutase Cu/Zn-superoxide dismutase and catalase in livers were all enhanced after 4 weeks of *Rhodiola rosea* supplementation especially at the dose of 125 mg per day per rat. Treatment of *Rhodiola rosea* extracts for 4 weeks significantly increased swimming performance.

In vitro

Li *et al*. (2011): In the present study the protective activity of salidroside against 1-methyl-4-phenylpyridinium (MPP(+)) -induced apoptosis in PC12 cells was investigated. The incubation of PC12 cells with salidroside prior to MPP(+) exposure reduced cell apoptosis and attenuated collapse of the mitochondrial membrane potential (MMP). Furthermore, salidroside inhibited the MPP(+)-induced nitric oxide (NO) increase and overexpression of nNOS and iNOS, and suppressed accumulation of reactive oxygen species (ROS) and intracellular free Ca(2+). The authors concluded that the results show that the protective effects of salidroside on PC12 cells are mediated, at least in part, by inhibition of the NO pathway.

Yu *et al*. (2010): The aim of this study was to investigate the effects of salidroside on hydrogen peroxide (H_2O_2)-induced cell apoptosis in nerve growth factor (NGF)-differentiated PC12 cells and the possible involvement of the extracellular signal-related protein kinase 1/2 (ERK1/2) signalling pathway. MTT assay, Hoechst 33342 staining, and TdT-mediated dUTP-biotin nick end labelling assay collectively showed that the pre-treatment with salidroside alleviated, in a dose-dependent manner, cell viability loss and apoptotic cell death induced by H_2O_2 stimulation in cultured NGF-differentiated PC12 cells. According to Western blot analysis, pre-treatment with salidroside transiently caused the activation of the ERK1/2 pathway; a selective inhibitor of the mitogen-activated protein kinase (MAPKK, MEK) blocked the salidroside-activated ERK pathway and thus attenuated the influences of salidroside on H_2O_2-induced increase in the level of cleaved caspase-3, a chief executant of apoptosis cascades. Morphological analysis further indicated that in the presence of the MEK inhibitor, the neuroprotective effect of salidroside against H_2O_2-evoked cell apoptosis was significantly abrogated. Taken together, the authors conclude that the results suggest that the neuroprotective effects of salidroside might be modulated by the ERK signalling pathway, especially at the level or upstream of the caspase-3 activation.

Tan *et al*. (2009): The protective effects of salidroside on endothelial cells apoptosis induced by the hypoxia mimicking agent cobalt chloride was investigated. After challenge with cobalt chloride for 24 hours, loss of cell viability and excessive apoptotic cell death were observed in EA.hy926 endothelial

cells, and the level of intracellular ROS increased concentration-dependently. However, the endothelial cell apoptosis and excessive ROS generation were attenuated markedly by salidroside pre-treatment. In addition, salidroside inhibited activation of caspase-3 and cleavage of poly(ADP-ribose) polymerase (PARP) induced by cobalt chloride, decreased expression of Bax and rescued the balance of pro- and anti-apoptotic proteins. According to the authors, these findings suggest that salidroside protects endothelial cells from cobalt chloride-induced apoptosis as an antioxidant and by regulating, the Bcl-2 family.

Chen *et al*. (2009a): This study investigated whether salidroside was able to extend its neuroprotection to primary cultured rat hippocampal neurons against hydrogen peroxide (H_2O_2)-induced cell damage. Cell viability tests and cell apoptosis assays confirmed that salidroside pre-treatment attenuated H_2O_2-stimulated apoptotic cell death in primary culture of hippocampal neurons in a concentration-dependent manner. The authors conclude that the measurements of caspase-3 activity, NO production, and NO synthase (NOS) activity suggest that the protection of salidroside, shown in this study, might be mediated by inhibiting caspase-3 activity, and antagonising NO production and NOS activity during H_2O_2 stimulation.

Mao *et al*. (2010): Salidroside reversed senescence-like phenotypes in the oxidant challenged model, including alterations of morphology, cell cycle, SA-β-gal staining, DNA damage, as well as related molecules expression such as p53, p21 and p16. The protection occurred in a dose-dependent manner, with 5μM offering best efficacy. The authors conclude that the proposed antioxidant property of the compound was confirmed in this cellular system, and thus at least partially accounted for the protection of the compound against premature senescence. Similar protection of salidroside against replicative senescence was observed as well. The regulation of senescence-related molecules by salidroside involved ROS-irrelevant mechanisms in both models.

Effects on the endocrinous system:

In vivo

Wang *et al.* (2009, only abstract available): The effects of salidroside on the function and ultramicro-pathological change of the hypothalamic-pituitary-gonadal (HPG) axis of male rats in experimental navigation and intensive exercise was investigated. Six-week Sprague Dawley (SD) rats were randomised into three groups: non-stress control (NC, n = 10), training control (TC, n = 12) and salidroside treatment (ST, n = 12) group. Blood samples were collected from the NC rats that did not receive any stimulus after a 7-day intragastric administration of saline. The TC rats underwent a 10-day running training with increasing load on the treadmill followed by a 7-day intragastric administration of saline. The ST rats were subjected to the same process of running training as the TC group and received intragastric administration of salidroside. Then blood samples were immediately obtained. The serum testosterone level was significantly lower in the TC than in the NC group but showed no difference between the ST and NC groups. HE staining revealed no difference in testis histopathology among the three groups. Ultramicro-pathology showed that the secretory granules of the pituitary cells were reduced in the TC rats compared with the NC ones; the number of the granules increased in the ST group compared with the TC rats; mitochondrial swelling, increase of electron density and decrease/disappearance of mitochondrial cristae were observed in the Leydig cells of the TC rats. No differences were found in the testicular cells between the ST and NC groups. It is concluded by the authors that negative psychological stress and intensive exercise can significantly suppress the function of the HPG axis in rats. Salidroside therapy may have protective effects on the HPG axis.

Neuroprotective effects:

In vitro

Chen *et al.* (2008b): This study aimed to evaluate the inhibitory effects of salidroside on glutamate-induced cell death in a primary culture of rat hippocampal neurons as compared to brain-derived neurotrophic factor (BDNF) as positive control. MTT and LDH assays, together with Hoechst 33342 staining, terminal deoxynucleotidyl transferase dUTP-mediated nicked end labelling (TUNEL) assay and flow cytometric analysis using annexin-V and propidium (PI) label, indicated that salidroside pre-treatment attenuated glutamate-induced apoptotic cell death in primary cultured hippocampal neurons, showing a dose-dependent pattern. Furthermore, caspase-3 activity assay and calcium measurements with Fluo 4-AM, respectively, revealed that salidroside pre-treatment antagonised activation of caspase-3 and elevation of intracellular calcium level, both of which were induced by glutamate stimulation.

Cao *et al.* (2006): Salidroside could protect PC12 cell against injuries caused by exposure of PC12 cells to 2 mmol/L glutamate for 15 minutes followed by incubation with serum-free medium for 24 hours, which resembled the excitotoxin *in vivo* system. Furthermore, salidroside could decrease the cytosolic free calcium concentration $[Ca^{2+}]i$ of PC12 cells in Mg^{2+}-free Hanks' solution and D-Hanks' solution but there was no effect on basal $[Ca^{2+}]i$ in Hanks' solution. The studies also indicated that salidroside inhibited the increases of $[Ca^{2+}]i$ induced by KCl and glutamate. In conclusion, salidroside may protect PC12 cells against glutamate excitotoxic damage through suppressing the excessive entry of Ca^{2+} and the release of the calcium stores.

Zhang *et al.* (2007): In this paper, the neuroprotective effects of salidroside on hydrogen peroxide H_2O_2-induced apoptosis in SH-SY5Y cells were investigated. Pre-treatment with salidroside markedly attenuated H_2O_2-induced cell viability loss and apoptotic cell death in a dose-dependent manner. The mechanisms by which salidroside protected neuron cells from oxidative stress included the induction of several antioxidant enzymes, thioredoxin, heme oxygenase-1, and peroxiredoxin-I; the down regulation of pro-apoptotic gene Bax and the up regulation of anti-apoptotic genes Bcl-2 and Bcl-X(L). Furthermore, salidroside dose-dependently restored H_2O_2-induced loss of mitochondrial membrane potential as well as the elevation of intracellular calcium level. The authors conclude that these results suggest that salidroside has protective effects against oxidative stress-induced cell apoptosis, which might be a potential therapeutic agent for treating or preventing neurodegenerative diseases implicated with oxidative stress.

Zhang *et al.* (2010): Beta-amyloid (Aβ) peptide, the hallmark of Alzheimer's disease (AD), invokes a cascade of oxidative damages to neurons and eventually leads to neuronal death. In this study, salidroside was investigated to assess its protective effects and the underlying mechanisms against Aβ-induced oxidative stress in SH-SY5Y human neuroblastoma cells. $Aβ_{25-35}$-induced neuronal toxicity was characterised by the decrease of cell viability, the release of LDH, morphological alterations, neuronal DNA condensation, and the cleavage of poly(ADP-ribose) PARP by activated caspase-3. Pre-treatment with salidroside markedly attenuated $Aβ_{25-35}$-induced loss of cell viability and apoptosis in a dose-dependent manner. The mechanisms of salidroside protection of neurons from oxidative stress included the induction of antioxidant enzymes, thioredoxin, heme oxygenase-1 (HO-1), and peroxiredoxin-I; the down regulation of pro-apoptotic protein Bax and the upregulation of anti-apoptotic protein Bcl-X(L). Furthermore, salidroside dose-dependently restored $Aβ_{25-35}$-induced loss of MMP as well as suppressed the elevation of intracellular ROS level. It was also observed that Abeta(25-35) stimulated the phosphorylation of mitogen-activated protein (MAP) kinases, including c-Jun NH(2)-terminal kinase (JNK) and p38 MAP kinase, but not extracellular signal-regulated kinase1/2 (ERK1/2). Salidroside inhibited $Aβ_{25-35}$-induced phosphorylation of JNK and p38 MAP kinase, but not ERK1/2. In the opinion of the authors these results suggest that salidroside has protective effects against $Aβ_{25-35}$-

induced oxidative stress, which might be a potential therapeutic agent for treating or preventing neurodegenerative diseases.

Yu *et al.* (2008): The hypoglycaemia and serum limitation-induced cell death in cultured PC12 cells represents a useful *in vitro* model for the study of brain ischemia and neurodegenerative disorders. In this study, MTT assay, Hoechst 33342 staining, and flow cytometry with annexin V/PI staining collectively showed that pre-treatment with salidroside attenuated, in a dose-dependent manner, cell viability loss, and apoptotic cell death in cultured PC12 cells induced by hypoglycaemia and serum limitation. RT-PCR, Western blot analysis, and enzymatic colorimetric assay indicated the changes in expression levels of Bcl-2, Bax, and caspase3 in PC12 cells on exposure to hypoglycaemia and serum limitation with and without salidroside pre-treatment, respectively. Rhodamine 123 staining and flow cytometry with 2',7'-Dichlorofluorescin diacetate staining revealed the changes in the mitochondrial membrane potential and radical ROS production in PC12 cells on exposure to hypoglycaemia and serum limitation with and without salidroside pre-treatment, respectively. The authors propose that the experimental results suggest that salidroside protects the PC12 cells against hypoglycaemia and serum limitation-induced cytotoxicity possibly by the way of the modulation of apoptosis-related gene expression, the restoration of the mitochondrial membrane potential, and the inhibition of the intracellular ROS production.

Cardioprotective effects:

In vitro

Wu *et al.* (2009): The modification of proteins with O-linked N-acetylglucosamine (O-GlcNAc) is increasingly recognised as an important posttranslational modification that modulates cellular function. Cardiomyocytes were exposed to 4 hours of ischemia and 16 hours of reperfusion, and then cell viability, apoptosis, glucose uptake, ATP levels and cytosolic Ca^{2+} concentration were determined, and O-GlcNAc levels were assessed by Western blotting. Salidroside (80 μM) was added 24 hours before ischemia/reperfusion was induced. Treatment with salidroside improved cell viability from 64.7+/-4.5% to 85.8+/-3.1%, decreased LDH release from 38.5+/-2.1% to 21.2+/-1.7%, reduced cell apoptosis from 27.2+/-3.2% to 12.2+/-1.9%, improved cardiomyocytes glucose uptake by 1.7-fold and increased O-GlcNAc levels by 1.6-fold, as well as reducing cytosolic Ca^{2+} concentration compared to untreated cells following ischemia/reperfusion. Furthermore, the improved cell survival and the increase in O-GlcNAc with salidroside were attenuated by alloxan, an inhibitor of O-GlcNAc transferase. The authors conclude that tese results suggested that salidroside significantly enhances glucose uptake and increases protein O-GlcNAc levels and this is associated with decreased cardiomyocytes injury following ischemia/reperfusion.

Zhang *et al.* (2009): The study was aimed to investigate the cardioprotective role of salidroside and the underlying mechanisms in hypoxia-induced cardiomyocyte death. Cardiomyocytes pretreated with or without salidroside for 24 hours were exposed to hypoxic condition for 6 hours and then cell viability, necrosis, apoptosis, the expressions of hypoxia inducible factor HIF-1α and vascular endothelial growth factor (VEGF) were investigated. Pre-treatment with salidroside attenuated hypoxia-induced cell viability loss, cell necrosis and apoptosis in a dose-dependent manner. Mechanistically, pre-treatment with salidroside up-regulated the HIF-1 α protein expression and induced its translocation. Moreover, the level of VEGF, a downstream target of HIF, was increased in parallel with the level of HIF-1 α following pre-treatment with salidroside. However, 2-methoxyestradiol (2-ME2), a HIF-1 α inhibitor, attenuated the protection of salidroside and blocked the increase of HIF-1 α and VEGF. The authors state that these data indicated that salidroside has protective effect against hypoxia-induced cardiomyocytes necrosis and apoptosis by increasing HIF-1 α expression and subsequently up-regulating VEGF levels.

Zhong *et al.* (2010): The cardioprotective effects of salidroside, isolated from *Rhodiola rosea* L., on oxygen-glucose deprivation (OGD)-induced cardiomyocyte death and ischemic injury evoked by acute myocardial infarction (AMI) was investigated in rats. Pre-treatment with salidroside notably ameliorated cell viability losses in a dose-dependent manner and in parallel it alleviated morphologic injury detected by electron microscopy. Mechanistically, diminished OGD-induced cardiomyocyte apoptosis was shown in salidroside-pre-treated cardiomyocytes, in accordance with minimal ROS burst. Moreover, salidroside markedly upregulated the Bcl-2/Bax ratio and preserved mitochondrial transmembrane potential. Salidroside administration also inhibited myocardial apoptosis in AMI rats by increasing phosphorylation of AKT and decreasing activation of caspase-3. These findings, according to the authors, suggest that salidroside reduced ischemia-mediated myocardial damage.

Effects on the blood system:

In vitro

Qian *et al.* (2011): This study attempted to examine the potential erythropoiesis-stimulating and anti-oxidative effect of salidroside in TF-1 erythroblasts. The erythropoiesis-promoting effect was determined by treating human TF-1 cells with salidroside in the presence and absence of erythropoietin (EPO) through the measurement of the expression of a series of erythroid markers such as glycophorin A (GPA), transferrin receptor (CD71) and hemoglobin (Hb). The potential protective effect of salidroside against H_2O_2-induced apoptosis and its underlying mechanism in TF-1 erythroblasts were examined by flow cytometry and Western blot analysis. The authors concluded that salidroside promotes erythropoiesis in the EPO-treated cells and it also reduces the number of apoptotic cells in TF-1 erythroblasts after H_2O_2 treatment probably through the up-regulation of protective proteins thioredoxin-1 and glutathione peroxidase-1.

Effects on metabolism:

In vitro

Kobayashi *et al.* (2008): As a methanol extract of the rhizome of *Rhodiola rosea* inhibits the activity of lipase in isolated mouse plasma *in vitro* and in the mouse gastrointestinal tube *in vivo*, the active components in this plant were investigated. After fractionation and separation processes, rhodionin and rhodiosin were isolated as active ingredients. Their IC_{50} values were 0.093 mM and 0.133 mM *in vitro*, respectively. Both compounds suppressed the elevation of the postprandial blood triglyceride level, e.g., by 45.6% (150 mg per kg, 60 minutes after oral administration) and 57.6% (200 mg per kg, 180 minutes after oral administration), respectively.

Li *et al.* (2008): The metabolic effects of salidroside on skeletal muscle cells were investigated. Salidroside dose-dependently stimulated glucose uptake in differentiated L6 rat myoblast cells. Inhibition of AMP-activated protein kinase (AMPK) by pre-treating the cells with compound C (= dorsomorphin) potently reduced salidroside-stimulated glucose uptake, while inhibition of phosphatidylinositol 3-kinase (PI3K) by wortmannin exhibited no significant inhibitory effect on salidroside-mediated glucose transport activation. Western blotting analyses revealed that salidroside increased the phosphorylation level of AMPK and acetyl-CoA carboxylase (ACC). In addition, salidroside enhanced insulin-mediated AKT activation and glucose uptake, and such enhancement can be specifically inhibited by compound C.

Effects on neuraminidase:

Jeong *et al*. (2009): The flavonols kaempferol, herbacetin, rhodiolinin, rhodionin and rhodiosin were isolated from *Rhodiola rosea*. The compounds showed neuraminidase inhibitory activities with IC_{50} values ranging from 1.4 to 56.9 µM. The *in vitro* anti-influenza virus activities were evaluated using

two influenza viral strains, H1N1 (A/PR/8/34) and H9N2 (A/Chicken/Korea/MS96/96), testing their ability to reduce virus-induced cytopathic effect (CPE) in MDCK cells. The activity of these compounds ranged from 30.2 to 81.9 µM against H1N1- and 18.5 to 49.6 µM against H9N2-induced CPE. Activity depended on the position and number of hydroxy groups on the flavonoids backbone.

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

A high number of pharmacological investigations on herbal preparations and isolated constituents from the underground parts of *Rhodiola rosea* are published. Some of the studies (e.g. in models investigating anti-fatigue effects, stress-protective effects) indicate a possible relation to the traditional medicinal use. Results from studies performed with isolated constituents suggest that the phenylethanoids like salidroside contribute to these effects.

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

In vitro

Thu *et al*. (2016): Six commercially available products containing *Rhodiola rosea* were tested on the isolated enzymes CYP3A4, CYP2D6 and CYP1A2. The herbal preparations in these products are not described in detail, the authors found significant differences with regard to concentrations of typical constituents. Ethanolic extracts of all products inhibited all tested enzymes, the strongest inhibition was found for a tincture and CYP3A4 with an IC_{50} value of 7.2 µg/ml. The authors admit that an extrapolation of these results to the human situation is difficult.

In a subsequent study (Thu *et al*., 2017) the authors investigated the influence of a commercial herbal preparation (no further details) on isolated human CYP2C9. An ethanolic extract of the tablets inhibited CYP2C9 with an IC_{50} value of 19.2 µg/ml.

Xu *et al*. (2013) investigated isolated constituents with regard to their inhibitory effect on CYP2D6. Rhodiosin and rhodionin showed non-competitive inhibitory activity with IC_{50} values of 0.761 µM and 0.42 µM, respectively.

Hellum *et al.* (2010) investigated six clones of *Rhodiola rosea* from different areas in Norway for their *in vitro* inhibitory potential on CYP3A4-mediated metabolism and P-gp efflux transport activity. Extracts were prepared using ethanol 96% as a primary extraction solvent, the dry residue was re-dissolved in ethanol 50%, the supernatant was used for the experiments. C-DNA baculovirus expressed CYP3A4 and Caco-2 cells were used for inhibitory assays, and as positive control inhibitors ketoconazole and verapamil were applied, respectively. Scintillation counting was used to quantify the transport of (3)H-digoxin in Caco-2 cells. All clones showed potent inhibition of CYP3A4 and P-gp activities, with IC_{50} values ranging from 1.7 to 3.1 µg/ml and from 16.7 to 51.7 µg/ml, respectively. The concentration of presumed biologically active constituents in the different clones varied considerably, but this variation was not related to the clones' inhibitory potential on CYP3A4 or P-gp activities.

In vivo

Panossian *et al*. (2010) found that in rats the bioavailability of rhodioloside was high after oral administration (75-90%) compared to that of rosavine (20-26%). After intravenous application rhodioloside was 1 hour after administration no longer detectable in the plasma. After multiple single doses (50 mg per kg on 5 consecutive days) the maximum concentration of rhodioloside in the plasma was reached 1-1.5 hours after the administration of the herbal preparation SHR-5. After 5 hours the blood level fell below the limit of detection.

Panossian *et al.* (2009) investigated whether *Rhodiola rosea* SHR-5 extract (DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water) interacts with warfarin and theophylline when administered concomitantly. The extract used in the theophylline study contained 2.7% rhodioloside (= salidroside), 6.0% rosavin and 0.8% tyrosol, while that for the warfarin study contained 2.5% rhodioloside, 3.9% rosavin and 0.8% tyrosol. The Wistar rats received orally 50 mg per kg daily for 3 days. After the final dose the animals received a single dose of aminophylline or warfarin. The animals in the placebo group received water by oral gavage. All relevant pharmacokinetic parameters remained unchanged. The authors conclude that the concomitant treatment of rats with theophylline and SHR-5 did not give rise to significant effects on the pharmacokinetics of theophylline. Simultaneous administration of SHR-5 and warfarin did not significantly alter the pharmacokinetics or the anticoagulant activity of warfarin.

Spanakis *et al.* (2013) investigated in a cross over design the influence of *Rhodiola rosea* on the metabolism of losartan in six healthy female rabbits. The herbal preparation is insufficiently characterised, it contained 8 mg rosavines / 250 mg extract. 3 rabbits received losartan alone, the other 3 received the combination of losartan and *Rhodiola rosea*. After a wash-out period of 1 week the design was reversed. Losartan was dosed with 5 mg per kg, Rhodiola product with 50 mg per kg. An almost 2-fold increase in the AUC of losartan was observed, while no significant influence on the pharmacokinetic parameters on the active metabolite EXP3174 was detected.

Assessor's comment:

Non-clinical interaction studies indicate a potential inhibition of CYP enzymes. Interactions are further evaluated in section 5.5.4.

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

3.3.1. Single dose toxicity

A possible CNS toxicity was investigated by Hancke *et al.* (1993, unpublished). Mice received 100 mg per kg or 500 mg per kg of the herbal preparation SHR-5 intraperitoneally. The influence of the study medication was rated according to the 'Irwin Method', which utilises several behavioural, neurological and autonomic parameters as well as mortality. No signs of toxicity were observed.

Unpublished tests on the cytotoxicity (inhibitory cell growth with L1210 cells and colony-forming efficiency with V79 cells) of the powdered underground organs (Bjellin *et al*., 1988) revealed a very low cytotoxic potential.

The considerably high dosages which were used in some of the pharmacological tests (e.g. Chen *et al*., 2008a only abstract available, Qu *et al*., 2009) indicate that dosages up to 6 g herbal preparation per kg body weight per day were well tolerated in rats.

3.3.2. Repeat dose toxicity

The Swedish Herbal Institute supplied unpublished information (Burgos & Hancke 1991) regarding tests on the subchronic toxicity of the herbal preparation SHR-5. The herbal preparation was administered orally to rats for 90 days in a dose range from 1.0 – 3.4 g per kg. The study medication did not change the development of the body weight, behaviour and appearance of the test animals. Further parameters were not investigated.

In a subsequent study Hancke & Burgos (1992, unpublished) investigated the same herbal preparation in dosages of 0.142 – 1.43 g per kg in piglets for 90 days. No changes in haematological parameters were observed, also glucose, triglyceride, creatinine kinase and urea levels as well as protein concentrations remained unchanged. An increase in hepatic transaminases was attributed to the increasing hepatic enzyme activity during maturation of the piglets.

3.3.3. Genotoxicity

In a Public Assessment Report of the MHRA it is stated that an extract prepared with ethanol 68% V/V did not reveal any mutagenic effect up to a cytotoxic concentration of 3,160 µg/plate in an Ames test, with and without metabolic activation. No more data are available.

Zhu *et al.* (2010, only abstract available) evaluated the potential genotoxicity of salidroside by using the standard battery of tests (i.e., bacterial reverse mutation assay, chromosomal aberrations assay, and mouse micronucleus assay). The results showed that salidroside was not genotoxic under the conditions of the reverse mutation assay, chromosomal aberrations assay, and mouse micronucleus assay conditions. The anticipated clinical dose seems to be smaller compared to doses administered in the genotoxicity assays.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

No data available.

3.3.8. Conclusions on toxicological data

Limited data regarding toxicity do not indicate special concerns.

3.4. Overall conclusions on non-clinical data

A high number of pharmacological investigations on herbal preparations and isolated constituents from the underground parts of *Rhodiola rosea* are published. However, in many of the experiments concentrations or dosages far exceeding the proposed dose in humans were applied. Therefore the clinical relevance of the results of such studies are considered not known.

Some of the studies (e.g. in models investigating anti-fatigue effects, stress-protective effects) support the medicinal use of herbal preparations from *Rhodiola rosea* as an adaptogen and make the use in this indication plausible. Results from studies performed with isolated constituents suggest that the phenylethanoids like salidroside contribute to these effects.

Only limited data is published on toxicity of preparations of *Rhodiola*. Non-clinical interaction studies indicate a potential inhibition of CYP enzymes. Interactions are further evaluated in section 5.5.4.

Tests on reproductive toxicity, genotoxicity and carcinogenicity are not available. As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

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

The purpose of a study by Parisi *et al.* (2010, only abstract available) was to investigate the effects on physical performance as well as on the redox status of a chronic *Rhodiola rosea* supplementation in a group of competitive athletes during endurance exercise. Following a chronic supplementation with *Rhodiola rosea* for 4 weeks (no details on the type of the herbal preparation available), 14 trained male athletes underwent a cardio-pulmonary exhaustion test, additionally blood samples were evaluated for antioxidant status and other biochemical parameters. These data were compared with those coming from the same athletes after an intake of placebo. The supplementation did not affect the maximum heart rate, Borg Scale level (measure for perceived exertion), peak oxygen uptake, blood antioxidant status, inflammatory parameters and blood glucose level. The level of plasma free fatty acids was significantly reduced. Blood lactate and plasma creatine kinase levels were found to be significantly lower ($p<0.05$) in treated subjects when compared to the placebo treated group.

Evdokimov (2009, only abstract available, original article in Russian language): Seven-hour continuous physical loading test (bicycle ergometry) was used to assess the effects of a cryopowder of *Rhodiola rosae* on the human cardiorespiratory system. Comparing with the control, according to the author, the preparation facilitated activation of the energy-supplying mechanisms in human organism during physical work. In addition, it increased the efficiency of the cardiovascular and respiration systems and prevented fatigue growth.

Skarpanska-Steijnborn *et al.* (2009) investigated the effect of *Rhodiola rosea* supplementation on the balance of oxidants and antioxidants in the serum and erythrocytes of competitive rowers. The study medication contained 100 mg of a *Rhodiola rosea* 'concentrate' (no more details available) and 5 mg zinc and was given twice daily for 4 weeks. This double-blinded study included 22 members of the Polish Rowing Team who were participating in a preparatory camp. At the beginning and end of the study, participants performed a 2,000-m maximum test on a rowing ergometer. Blood samples were taken from the antecubital vein before each exercise test, 1 minute after completing the test, and after a 24-hours restitution period. The following redox parameters were assessed in erythrocytes: superoxide dismutase activity, glutathione peroxidase activity, and thiobarbituric-acid-reactive substances concentrations. In addition, creatine kinase activity and total antioxidant capacity were measured in plasma samples, lactate levels were determined in capillary blood samples, and uric acid concentrations were measured in serum. After supplementation, the total plasma antioxidant capacity was significantly higher ($p=0.0002$) in the supplemented group than in the placebo group, and

superoxide dismutase activity in erythrocytes directly after and 24 hours after the ergometry was significantly (p=0.0461) lower in athletes receiving *Rhodiola rosea* extracts than in the placebo group.

The purpose of the investigation by Walker *et al.* (2007) was to examine the effect of *Rhodiola rosea* ingestion on human skeletal muscle phopshocreatine recovery after exhaustive exercise. The study medication was 1500 mg *Rhodiola rosea* standardised to 3% rosavins (no more details on the herbal preparation available), divided into 3 doses. Twelve resistance-trained men (19 to 39 years of age) completed incremental forearm wrist flexion exercise to volitional fatigue, once after ingesting *Rhodiola rosea* for 4 days, and once after ingesting an equivalent placebo dose. During exercise and recovery from exercise, muscle phosphates were examined using ^{31}P nuclear magnetic resonance spectroscopy. In summary, there were no significant differences between groups for any of the parameters measured. The authors conclude that *Rhodiola rosea* ingestion does not improve ATP turnover during or immediately after exercise.

In a double-blind, placebo-controlled study Abidov *et al.* (2004) studied the effect of 30 mg *Rhodiola rosea* extract (no details available) twice daily for 30 days before and 6 days after exhausting physical exercise on the level of C-reactive protein and creatinine kinase. The authors report that the study medication reduced the levels of C-reactive protein compared to both placebo and control group.

Wing *et al.* (2003) investigated the effects of a 7-day supplementation with 447 mg *Rhodiola rosea* 4 times daily (no details on the herbal preparation) on hypoxia and oxidative stress at a simulated altitude of 4600 m. Fifteen volunteers (ages 20-33) received 3 separate 60-minute hypoxic exposures by breathing 13.6% oxygen at an ambient barometric pressure of 633 mm Hg (simulating the partial pressure of oxygen at 4600 m elevation). Each subject received, in random order, treatments of a 7-day supply of placebo, *Rhodiola rosea*, and an acute dose of stabilised oxygen dissolved in water. The supplementation did not have a significant effect on blood oxygenation after 60 minutes of sedentary hypoxic exposure. Hypoxia-induced oxidative stress was observed in the control group only. The authors conclude that the supplementation appeared not to increase oxidative stress and may decrease free radical formation after hypoxic exposure compared with the control.

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

Sixteen volunteers received in a single dose 288 mg of the herbal preparation SHR-5 containing 7.26 mg rhodioloside and 8.4 mg rosavine (Panossian *et al*., 2010). Rhodioloside was detectable immediately after oral administration while rosavin could not be detected in the first hour. Maximum concentrations were reached 2 hours after oral administration (C_{max} rhodioloside 948 ng/ml, rosavin 446 ng/ml). After 8 hours the concentration had fallen below the detection limit.

4.2. Clinical Efficacy

4.2.1. Dose response studies

Darbinyan *et al.* (2007): see details in 4.2.2.

Shevtsov *et al.* (2003): see details in 4.2.2.

4.2.2. Clinical studies (case studies and clinical trials)

Clinical trials: Indication mental performance, fatigue

Olsson *et al.* (2009): The aim of the study was to assess the efficacy of the extract SHR-5 (DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water) in the treatment of

individuals suffering from stress-related fatigue. The phase III clinical trial took the form of a randomised, double-blind, placebo-controlled study with parallel groups. Participants, males and females aged between 20 and 55 years, were selected according to the Swedish National Board of Health and Welfare diagnostic criteria for fatigue syndrome. A total of 60 individuals were randomised into two groups, one (N = 30) of which received four tablets daily of SHR-5 extract (576 mg extract/per day), while a second (N = 30) received four placebo tablets daily. The effects of the extract with respect to quality of life (SF-36 questionnaire, a validated scale to assess the quality of life), symptoms of fatigue (Pines' burnout scale), depression (Montgomery-Asberg depression rating scale - MADRS), attention (Conners' computerised continuous performance test II - CCPT II), and saliva cortisol response to awakening were assessed on day 1 and after 28 days of medication. Data were analysed by between-within analyses of variance. The primary endpoint (Pine's burnout scale) was in the treatment group (n=29) changed from 4.27±0.54 to 4.01±0.58 and in the placebo group (n=30) changed from 4.33±0.56 to 4.26±0.51 (p=0.047).

Assessor's comment:

Due to the small sample size this clinical trial does not support well-established use.

Schutgens *et al.* (2009): In a randomised double blind placebo-controlled pilot study, 30 healthy subjects were randomly assigned to three groups: one group (n = 10) taking placebo pills, one group (n = 10) taking *Rhodiola rosea* (144 mg extract SHR-5, DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water) pills and one group (n = 10) taking ADAPT-232 supplements (fixed combination of *Eleutherococcus senticosus*, *Rhodiola rosea* (SHR-5 extract, no details on the amount of extract per tablet) and *Schisandra chinensis*). The study medication was given twice daily for 7 days. All subjects underwent measurements to determine ultra-weak photon emission (UPE) of the dorsal side of their hands using a photon-counting device, both before and after a week of taking the supplements. In addition, the experienced levels of stress and fatigue (tiredness) were evaluated. After 1 week of supplementation, the *Rhodiola* group showed a significant decrease (p=0.027) in photon emission in comparison with the placebo group. Furthermore, after supplementation, a significant decrease (p=0.049) concerning the experienced level of fatigue in the *Rhodiola* group was observed compared with the placebo group. No significant changes were observed between the ADAPT-232 and the placebo group.

Assessor's comment:

This pilot study evaluated in healthy subjects the subjectively experienced level of fatigue. A possible clinical relevance cannot be evaluated from the data. Due to the small sample size, healthy subjects and the not validated self-estimation of fatigue this clinical trial does not qualify the respective herbal preparation for well-established use.

De Bock *et al.* (2004): The purpose of this study was to investigate the effect of acute and 4-week *Rhodiola rosea* extract (no details on DER and extraction solvent, extract contains 3% rosavin and 1% salidroside) intake on physical capacity, muscle strength, speed of limb movement, reaction time, and attention in 24 healthy students. PHASE I: A double blind placebo-controlled randomised study (n=24) was performed, consisting of 2 sessions (2 days per session). Day 1: one hour after acute *Rhodiola rosea* intake (R, 200-mg *Rhodiola rosea* extract) or placebo (P, 700 mg starch) speed of limb movement (plate tapping test), aural and visual reaction time, and the ability to sustain attention (Fepsy Vigilance test) were assessed. Day 2: Following the same intake procedure as on day 1, maximal isometric knee-extension torque and endurance exercise capacity were tested. Following a 5-day washout period, the experimental procedure was repeated, with the treatment regimens being switched between groups (session 2). PHASE II: A double blind placebo-controlled study (n = 12) was performed. Subjects underwent sessions 3 and 4, identical to Phase I, separated by a 4-week R/P intake, during which subjects ingested 200 mg R/P per day. Compared with placebo the acute intake of

Rhodiola extract in Phase I increased ($p<0.05$) time to exhaustion from 16.8 +/- 0.7 minutes to 17.2+/- 0.8 minutes. Accordingly, VO2peak ($p<0.05$) and VCO2peak ($p<0.05$) increased during the study medication compared to placebo from 50.9 +/- 1.8 ml x min(-1) x kg(-1) to 52.9 +/- 2.7 ml x min(-1) x kg(-1) (VO2peak) and from 60.0 +/- 2.3 ml x min(-1) x kg(-1) to 63.5+/- 2.7 ml x min(-1) x kg(-1) (VCO2peak). Pulmonary ventilation ($p=0.7$) tended to increase more in the verum group compared to placebo (P: 115.9 +/- 7.7 L/min; R: 124.8 +/- 7.7 L/min). All other parameters remained unchanged. Four-week intake of *Rhodiola* did not alter any of the variables measured. The authors conclude that acute *Rhodiola rosea* intake can improve the endurance exercise capacity in young healthy volunteers. This response was not altered by prior daily 4-week *Rhodiola* intake.

Assessor's comment:

Due to the improperly characterised herbal preparations and the very small sample size of healthy subjects, this clinical trial cannot be used to support well-established use.

Shevtsov *et al.* (2003): A randomised, double-blind, placebo-controlled, parallel-group clinical study with an extra non-treatment group was performed to measure the effect of a single dose of standardised SHR-5 (DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water) on capacity for mental work against a background of fatigue and stress. Some physiological parameters, e.g. pulse rate, systolic and diastolic blood pressure, were also measured. The study was carried out on a highly uniform population comprising 161 healthy cadets aged from 19 to 21 years. Group 1 (41 subjects) received 370 mg extract per day, group 2 (20 subjects) received 555 mg extract per day. According to the authors, the study showed a pronounced anti-fatigue effect reflected in an anti-fatigue index defined as a ratio called AFI. The verum groups had AFI mean values of 1.0385 and 1.0195, 2 and 3 capsules respectively, whilst the figure for the placebo group was 0.9046. This was statistically significant ($p<0.001$) for both doses (verum groups), whilst no significant difference between the two dosage groups was observed. The authors state that there was a possible trend in favour of the lower dose in the psychometric tests. No such trend was found in the physiological tests. Only one case of hypersalivation in the placebo group was reported as undesirable effect.

Assessor's comment:

The trial was performed with healthy subjects. Moreover the tests used for the evaluation of the effects are not validated. Therefore this study does not allow to conclude on clinically relevant effects in patients.

Darbinyan *et al.* (2000): The aim of this study was to investigate the effect of repeated low-dose treatment with a standardised extract SHR-5 (DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water) on fatigue during night duty among a group of 56 young, healthy physicians. The effect was measured as total mental performance calculated as Fatigue Index. The tests chosen reflect an overall level of mental fatigue, involving complex perceptive and cognitive cerebral functions, such as associative thinking, short-term memory, calculation and ability of concentration, and speed of audio-visual perception. These parameters were tested before and after night duty during three periods of two weeks each: a) a test period of one *Rhodiola*/placebo tablet daily, b) a washout period and c) a third period of one placebo/Rhodiola tablet daily, in a double-blind cross-over trial. The verum tablets contained 170 mg extract (with approximately 4.5 mg salidroside) and were taken once daily. The perceptive and cognitive cerebral functions mentioned above were investigated using 5 different tests. A statistically significant improvement in these tests was observed in the treatment group during the first two weeks period. No side-effects were reported for either treatment. The authors propose that these results suggest that Rhodiola can reduce general fatigue under certain stressful conditions.

Assessor's comment:

The trial was performed with healthy subjects. Moreover the tests used for the evaluation of the effects are not validated. Therefore this study does not allow to conclude on clinically relevant effects in patients.

Spasov *et al.* (2000): The objective was to investigate the stimulating and normalising effect of the adaptogen *Rhodiola rosea* extract SHR-5 (DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water) in 40 students during a stressful examination period. The study was performed as a double-blind, randomised and placebo-controlled with low repeated dose regime. One tablet contained 50 mg of the *Rhodiola* extract, taken twice daily for 20 days. The physical and mental performance were assessed before and after the period, based on objective as well as on subjective evaluation. The most significant improvement in the SHR-5 group was seen in physical fitness, mental fatigue and neuro-motoric tests ($p<0.01$). The self-assessment of the general well-being was also significantly ($p<0.05$) better in the verum group. No significance was seen in the correction of text tests or a neuro-muscular tapping test.

Assessor's comment:

The trial was performed with a small sample of healthy subjects. Therefore this study does not allow to conclude on clinically relevant effects in patients.

Spasov *et al.* (2000a): 60 male students (17-18 years of age) were randomised to three groups; the participants in one group received the study medication (660 mg of Rhodiola, no details on the type of the herbal preparation published) for 20 days. The authors observed in the treatment group improvement of health and well-being, activeness level, mood, and work stimulation as well as reduced signs of fatigue. No adverse events in the verum group were observed.

Assessor's comment:

Because of the lack of any information concerning the type of the herbal preparation and the posology the findings cannot be taken into consideration.

Open studies:

Edwards et al. (2012): In an open-label study 101 subjects with life-stress symptoms received 2 times 200 mg extract (dry extract (1.5-5:1), extraction solvent ethanol 60% m/m) per day for 4 weeks. The effect was assessed using seven different questionnaires. The authors conclude that the treatment resulted in clinically relevant improvements of stress symptoms.

Bachmann (2016): In the frame of a non-interventional study 82 patients received 2 times 200 mg extract (dry extract (1.5-5:1), extraction solvent ethanol 60% m/m) per day for 4 weeks. The authors observed an onset of improvements of several stress parameters even on day 3 of the treatment, remaining or continuously improving over the treatment period.

Kasper & Dienel (2017): In a multicenter, open-label, exploratory clinical trial 118 outpatients suffering from burnout symptoms received 2 times 200 mg extract (dry extract (1.5-5:1), extraction solvent ethanol 60% m/m) per day for 12 weeks. Based on the evaluation of several questionnaires the authors conclude that the majority of the outcome measures improved after 1 week of treatment and continued to improve until the end of the study.

Lekomtseva et al. (2017): In an open-label study 100 subjects with prolonged or chronic fatigue symptoms received 2 times 200 mg extract (dry extract (1.5-5:1), extraction solvent ethanol 60% m/m) per day for 8 weeks. The exploratory data analysis revealed that the greatest change in symptoms was observed after 1 week, the fatigue symptoms declined further with statistically significance after 8 weeks.

Koop *et al*. (2020): In a single-arm, open label study 50 adult participants received 2 times 200 mg extract (dry extract (1.5-5:1), extraction solvent ethanol 60% m/m) for 12 weeks. Reaction times improved in the 'attention network task' as well as in other experimental neuropsychological tests. The authors conclude that an improvement in mental speed could be shown.

Clinical trials in other indications:

Darbinyan *et al.* (2007): The objective of this study was to assess the efficacy and safety of standardised extract SHR-5 (DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water) in patients suffering from a current episode of mild/moderate depression according to DSM-IV. The phase III clinical trial was carried out as a randomised double-blind placebo-controlled study with parallel groups over 6 weeks. The participants were males and females aged 18-70 years. The severity of the depression was determined by scores gained in Beck Depression Inventory and Hamilton Rating Scale for Depression (HAMD) questionnaires. Exclusion criteria: previous attempt to commit suicide, scores on the scales indicating suicidal tendency, total HAMD score above 31, progressive organic or metabolic brain syndrome, compulsive, schizophrenic or other delusive disorders. Patients with initial HAMD scores between 21 and 31 were randomised into three groups, one of which (group A: 31 patients) received two tablets daily of SHR-5 (340 mg per day), a second (group B: 29 patients) received two tablets twice per day of SHR-5 (680 mg per day), and a third (group C: 29 patients) received two placebo tablets daily. The efficacy of SHR-5 extract with respect to depressive complaints was assessed on days 0 and 42 of the study period from total and specific subgroup HAMD scores. For individuals in groups A and B, overall depression, together with insomnia, emotional instability and somatization, but not self-esteem, improved significantly following medication, whilst the placebo group did not show such improvements. In the group A the HAMD score improved from 24.52 to 15.97, in group B from 23.79 to 16.72, while it remained nearly unchanged in the placebo group (24.17 to 23.41). No serious side-effects were reported in any of the groups A-C.

No difference in the clinical outcome was observed between the different dosages.

Assessor's comment:

The observation of nearly an absent placebo-effect (expressed by a nearly unchanged HAMD score in the placebo group) is untypical for clinical trials with depressant patients. Therefore the significances documented in the publication remain questionable.

Bystritsky *et al.* (2008): The goal of this pilot study was to evaluate whether *Rhodiola rosea* is effective in reducing symptoms of generalised anxiety disorder (GAD). Ten participants (age 34-55 years) with a DSM-IV diagnosis of GAD were enrolled in this study. Participants received a total daily dose of 340 mg of *Rhodiola rosea* extract (no details of the type of the herbal preparation published) for 10 weeks. Assessments included the Hamilton Anxiety Rating Scale (HARS), the Four-Dimensional Anxiety and Depression Scale, and the Clinical Global Impressions of Severity/Improvement Scale. Individuals treated with *Rhodiola rosea* showed statistically significant decreases in mean HARS scores at endpoint ($t=3.27$, $p=0.01$). Adverse events were generally mild or moderate in severity, the most common being dizziness and dry mouth.

Cropley *et al.* (2015): In a non-controlled study 80 patients with mild symptoms of anxiety received 2 times 200 mg herbal preparation (dry extract (1.5-5:1), extraction solvent ethanol 60% m/m) per day. The authors observed a reduction in self-reported anxiety, stress, anger, confusion and depression.

Mao *et al.* (2015): In a phase II clinical trial 57 patients with major depressive disorder were randomised into three groups (placebo, *Rhodiola rosea* extract, sertraline). The patients received as single does 340 mg extract standardised to a content of 3.07% rosavin and 1.95% rhodioloside, or 50 mg sertraline or placebo. Depending on the effect after 2, 4 and 6 weeks of treatment the dosage was

increased up to 4-fold. The study duration was 12 weeks. The *Rhodiola*-treatment was less effective compared to sertraline, but fewer adverse events were reported.

Ha *et al.* (2002): The aim of the study was to investigate the changes of sleep architecture and blood oxygen saturation (SaO(2)) during sleep in men living at high altitude, and to investigate the effect of *Rhodiola* and acetazolamide on these sleep indexes. Twenty-four men aged 18 to 21 years who had stayed at high altitude (5.380 m above sea level) for 1 year were randomly divided into groups A (treated with oral *Rhodiola*, no information on kind of herbal preparation and on posology), B (treated with oral acetazolamide 0.25 g twice daily) and C (treated with Rhodiola + acetazolamide). Their sleep architecture and SaO(2) were recorded for 24 days before and after taking the medicines. The authors conclude that both Rhodiola and acetazolamide were effective in modulating the sleep architecture and improving the sleep quality in young men living at high altitude, but there was no synergistic effect between Rhodiola and acetazolamide.

Meta-analyses:

Hung *et al.* (2011): Eleven randomised controlled trials (RCTs) met the inclusion criteria, all were placebo-controlled (Shevtsov *et al.,* 2003, De Bock *et al.,* 2004, Abodiv *et al.,* 2004, Olsson *et al.,* 2009, Spasov *et al.,* 2000a, Spasoc *et al.,* 2000b, Darbinyan 2007, Darbinyan 2000, Walker 2007, Schutgens 2009, Wing 2003). Six trials investigated the effects of *Rhodiola rosea* on physical performance, four on mental performance, and two in patients diagnosed with mental health condition. The methodological quality of most trials was moderate or good. Only a few mild adverse events were reported. *Rhodiola rosea* may have beneficial effects on physical performance, mental performance, and certain mental health conditions. There is, however, a lack of independent replications of the single different studies. Five of the 11 RCTs reached more than three points on the Jadad score (i.e., good quality). More research seems warranted.

Blomkvist *et al.* (2009): With a focus on the statistical methods the authors found considerable shortcomings in all but one of the studies that claim significant improvement from roseroot extract. Overall, the study designs have not been well explained. Experimental results have been confused and appear to be in some cases incorrect. Some of the conclusions are based on selected results and contradicting data have not been adequately taken into account. For example it is criticised that Darbinyan *et al.* (2000) claimed significant results while insignificant results are explained away with unfounded assumptions. In the study of Darbinyan *et al.* (2007) irrelevant tests and an inappropriate statistical comparison were used. Bystritsky *et al.* (2008) and Fintelmann & Gruenwald (2007) claimed an effect but did not use a placebo control. In the article of Shevtsov *et al.* (2003) misprints and mix-ups occur. The authors find it alarming that poorly conceived and performed studies have been published apparently without adequate scientific and editorial scrutiny. The authors conclude that the currently available evidence for the claimed effects is insufficient and that the effect of *Rhodiola rosea* is in need of further investigation before therapeutic claims can be made.

Combination with vitamins and minerals:

Fintelmann & Gruenwald (2007) studied a food supplement containing 200 mg Rhodiola extract (no more details available), magnesium, vitamin E, vitamin B6, folic acid and vitamin B12 in a 12-week drug monitoring study. The study was neither blinded nor placebo controlled. The authors stated that in the 120 patients a statistically highly significant improvement in physical and cognitive deficiencies was observed. No adverse events occurred during the course of the study.

Table 5: Controlled clinical studies on humans with sufficiently characterised herbal preparations for the relief of symptoms of stress, such as fatigue and exhaustion.

Type	**Study**	**Test product(s)**	**Number of subjects**	**Type of subjects**	**Outcomes**	**Statistical analysis**	**Clinical relevance**
Olsson *et al.* (2009)	Phase III clinical trial; Randomised, double blind, placebo-controlled	DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water, 567 mg extract per day, duration of use: 28 days	30 patients verum (with 27 women), 30 patients placebo (with 27 women) Age: 20-55 years	Patients diagnosed with fatigue syndrome acc. to ICD	Primary endpoint: reduction in fatigue symptoms (Pine's burnout scale) was in the treatment group (n=29) changed from 4.27±0.54 to 4.01±0.58 and in the placebo group (n=30) changed from 4.33±0.56 to 4.26±0.51 (p=0.047)	Significance was defined with $p<0.05$	Small sample size, therefore, no conclusion on clinical relevance possible
Schutgens *et al.* (2009)	Randomised, double blind, placebo-controlled	288 mg extract SHR-5, DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water 7 days	10 patients placebo (with 5 female); 10 patients Rhodiola (with 5 females); 10 patients combination Eleutherococcus, Rhodiola,	Healthy subjects	Pilot study Subjective improvement of stress and tiredness according to a visual analogue scale	t-test	Pilot study Small sample size of healthy subjects, therefore no conclusion on clinical relevance possible

Type	Study	Test product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
			Schisandra (with 7 females) Age: mean 20 years				
Shevtsov *et al.* (2003)	Randomised, double-blind, placebo-controlled, parallel-group	370 or 555 mg extract SHR-5, DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water 6 weeks	Group 1: 41 subjects, 370 mg Group 2: 20 subjects: 555 mg Group 3: 40 subjects placebo Group 4: 20 subjects untreated control group Age: 19-21 years	Healthy male subjects	Improvement of an antifatigue index	Mann-Whitney test Student t-test	Healthy subjects; score not validated. No conclusion on clinical relevance possible
Darbinyan *et al.* (2000)	Randomised, double-blind, placebo-controlled, parallel-group	170 mg extract SHR-5, DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water 2 weeks	Group A: 26 subjects (with 14 females), age mean 25.5 years Group B: 30 subjects (with 19 females), age mean 27.3 years	Healthy subjects with non-specific fatigue	Improvements in Tests on the determination of speed of visual and audial perception	Student t-test	Small sample size of healthy subjects. Scores not validated. No conclusion on clinical relevance possible
Spasov *et al.* (2000)	Randomised, double-blind, placebo-controlled	100 mg extract SHR-5, DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water	20 subjects verum; 20 subjects placebo. Age: 17-19 years	Healthy male subjects	Improvement of physical fitness, mental fatigue and self-assessment of	Student t-test	Small sample size of healthy subjects. Scores not validated.

Type	Study	Test product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		20 days			general well-being		No conclusion on clinical relevance possible

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

No data published.

4.4. Overall conclusions on clinical pharmacology and efficacy

The results from trials on clinical pharmacology are contradictory. The dry extract (DER 2.5-5:1, extraction solvent 70% ethanol, second extraction solvent water) have been in medicinal use for more than 10 years in EU. However, the clinical studies to support clinical efficacy for the relief of symptoms of stress, such as fatigue and exhaustion, show methodological problems. Meta-analyses of these clinical trials found considerable shortcomings and deficiencies. Overall, it can be concluded that there is not sufficient evidence for a clinical efficacy of herbal preparations of *Rhodiola rosea* for the treatment of symptoms of fatigue or exhaustion. Therefore 'well-established use' cannot be supported in the monograph.

5. Clinical Safety/Pharmacovigilance

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

The safety data from clinical trials with herbal preparations similar or equal to the one in the EU herbal monograph are summarised in table 6 below.

Table 6: Clinical safety data from clinical trials

Reference	Study design	Test product(s)	Number of subjects	Type of subjects	Adverse events	Comments
Olsson *et al*. (2009)	Phase III clinical trial; Randomised, double blind, placebo-controlled	DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water, 567 mg extract per day, duration of use: 28 days	30 patients verum (with 27 women), 30 patients placebo (with 27 women) Age: 20-55 years	Patients diagnosed with fatigue syndrome acc. to ICD	No adverse events occurred during study period	No adverse events reported
Darbinyan *et al*. (2007)	Phase III clinical trial; Randomised, double blind, placebo-controlled	288 mg extract SHR-5, DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water 6 weeks	31 patients (with 21 females): 340 mg extract per day; 29 patients (with 17 females): 680 mg per day; 29 patients (with 15 females): placebo Age: 18-70 years	Patients with mild to moderate depression	No adverse events occurred during study period	No adverse events reported
De Bock *et al*. (2004)	Phase I: randomised, double blind, placebo-controlled Phase II: randomised, double blind	No information on DER and extraction solvent; extract containing 3% rosavin, 1% salidroside Phase I: two single doses with 5 days interval Phase II: 4 weeks	Phase I: 12 patients (with 6 females): 200 mg extract 12 patients (with 6 females): placebo Age: mean app. 21 years Phase II:	Healthy subjects	Phase I: 1 subject: headache Phase II: 1 subject: headache 1 subject: insomnia	The adverse events headache and insomnia further assessed in section 5.3.

Reference	Study design	Test product(s)	Number of subjects	Type of subjects	Adverse events	Comments
			6 patients (with 3 females): 200 mg extract 6 patients (with 3 females): placebo Age: mean app. 21 years			
Shevtsov *et al*. (2003)	Randomised, double-blind, placebo-controlled, parallel-group	370 or 555 mg extract SHR-5, DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water 6 weeks	Group 1: 41 subjects, 370 mg Group 2: 20 subjects: 555 mg Group 3: 40 subjects placebo Group 4: 20 subjects untreated control group Age: 19-21 years	Healthy male subjects	Placebo group: 1 subject hypersalivation No other adverse events	No adverse events reported in the verum group
Spasov *et al*. (2000a)	Randomised, controlled	660 mg extract (no further details) 20 days	20 subjects verum; 20 subjects placebo; 20 subjects: untreated control. Age: 17-19 years	Healthy male subjects	No adverse events	No adverse events reported
Edwards *et al*. (2012)	Open-label study	400 mg dry extract (1.5-5:1), extraction solvent ethanol 60% m/m 4 weeks	Baseline: 101 patients (with 68 females) Per protocol: 82 patients Age: 30-60 years	Subjects with life-stress symptoms	54 adverse events were recorded in 36 subjects 17 patients: nervous system disorders	Relative high number of reported adverse events; only MedDRA system organ class reported, no further details)

Reference	Study design	Test product(s)	Number of subjects	Type of subjects	Adverse events	Comments
					10 patients: gastrointestinal disorders 5 patients: psychiatric disorders No serious events	
Bachmann (2016)	Non-interventional study	400 mg dry extract (1.5-5:1), extraction solvent ethanol 60% m/m 4 weeks	82 subjects Age: 30-60 years	Patients with stress symptoms	No serious adverse events. Mild to moderate: nervousness, gastrointestinal complaints (no further details)	The adverse events nervousness and gastrointestinal complaints further assessed in section 5.3.
Kasper & Dienel (2017)	Open-label study	400 mg dry extract (1.5-5:1), extraction solvent ethanol 60% m/m 12 weeks	118 subjects (safety analysis set)(with 68 females) Age: 30-60 years	Patients with burnout symptoms	145 adverse events reported from 70 participants. Severity: 40.7% mild, 46.9% moderate, 12.4% severe. For 10.9% a causal relationship was rated as 'possible'. Head pressure, light-headedness, nausea, feeling irritated, eye swelling	Adverse events with 'possible' causal relationship reported. Head pressure, light-headedness, nausea, feeling irritated, eye swelling further assessed in section 5.3.
Lekomtseva *et al*. (2017)	Open-label	400 mg dry extract (1.5-5:1), extraction solvent ethanol 60% m/m	101 subjects (with 69 females), 1 drop out	Prolonged or chronic fatigue	41 subjects experienced a total of 44 adverse events	Nervous system disorders and gastrointestinal disorders further

Reference	Study design	Test product(s)	Number of subjects	Type of subjects	Adverse events	Comments
		8 weeks			Most of the study-related adverse events referred to nervous system disorders and the gastrointestinal system	assessed in section 5.3.
Cropley *et al*. (2015)	Randomised	400 mg dry extract (1.5-5:1), extraction solvent ethanol 60% m/m 2 weeks	39 subjects Rhodiola (with 20 females) 41 subjects untreated (with 28 females) Age: app. 21 years	Mildly anxious subjects	4 subjects reported adverse events: Forgetfulness, loss of appetite	Adverse events forgetfulness and loss of appetite further assessed in section 5.3.
Mao *et al*. (2015)	Phase II clinical trial Randomised, placebo-controlled	340 mg extract SHR-5, DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water 50 mg sertraline 12 weeks	20 subjects Rhodiola (with 8 females) 19 subjects sertraline (with 10 females) 18 subjects placebo (with 8 females) Age: app. 27-64 years	Subjects with mild to moderate depressive disorders	In the Rhodiola-group 2 participants reported nervousness, 2 reported dizziness	The adverse events nervousness and dizziness further assessed in section 5.3.

5.2. Patient exposure

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

5.3. Adverse events, serious adverse events and deaths

In table 6 in section 5.1, references that have studied and reported adverse events following the exposure to *Rhodiola rosea* are included. The adverse events reported in clinical studies for preparations and posologies in accordance with the monograph were mainly related to the SOCs nervous system disorders, gastrointestinal disorders and skin and subcutaneous tissue disorders.

De Bock *et al*. (2004) report that during phase I one participant receiving placebo experienced strong headache, while none of the 12 subjects receiving Rhodiola reported side effects. During phase II one participant in the placebo group experienced minor headache, in the Rhodiola group one subject reported moderate headache, another one insomnia.

In the study by Edwards *et al*. (2012), 101 patients were included in the safety analysis set. Overall, 54 adverse events were recorded in 36 subjects (35.6%). The most common adverse events were nervous system disorders (17 [16.8%] patients with 18 [33.3%] adverse events) and gastrointestinal disorders (10 [9.9%] patients with 10 [18.5%] adverse events), No serious adverse events were reported. Two subjects (2%) terminated the study prematurely because of adverse events (dizziness, abdominal distension). Both events were reported by the authors to have been assessed to be unlikely related to the study drug.

Bachmann (2016) reports from an non-interventional study including 82 patients mild to moderate gastrointestinal complaints and nervosity. No further details are provided.

Kasper & Dienel (2017) reported that in the safety analysis set (N=118) in total 145 adverse events from 70 participants (59.3%). 4 patients did not finalise the study due to adverse events. The most common adverse events were nervous system disorders 32/118 (27.1%), infections and infestations 32/118 (27.1%) and gastrointestinal disorder 15/118 (12.7%). Also skin and subcutaneous tissue disorders have been reported (5/46, 4.2%). For 5/46 patients (10.9%) a causal relationship was rated as 'possible' according to the authors i.e., head pressure, light-headedness, nausea, feeling irritated and eye swelling.

During the active treatment and the subsequent risk phase in the study by Lekomtseva *et al*. (2017), 41/101 (40.6%) subjects experienced a total of 44 AEs. None of the patients terminated the study prematurely because of adverse events. The largest number of adverse events referred to nervous system disorders (9/41 AEs), gastrointestinal disorders (8/41 AEs) and infections and infestations (7/41 AEs). However, most of the adverse events (32/44) were assessed as 'not related' to the study medication. In 12/44 adverse events a causal relationship with the study drug could not be excluded but was assessed as 'unlikely'.

Cropley *et al*. (2015) reported that out of the 40 subjects that were randomised to the treatment group, 4 subjects reported one treatment emergent adverse event each. Two of these adverse events were known symptoms of the condition under investigation, the other two reports have been related to an independent concomitant condition.

In addition, for another preparation in a study by Mao *et al*. (2015), 2 participants reported nervousness and 2 reported dizziness.

Svedlund *et al*. (2017, supplementary information) published adverse reactions for herbal medicinal products and natural remedies which were reported to the Swedish Medical Products Agency in the years 2007-2015. For Rhodiola 1 serious report (asthenia, dizziness, fatigue, headache, learning disorder, memory impairment, nausea) and 4 non-serious reports (anxiety, pruritus, tremor, headache, nausea, malaise) were received.

In the EudraVigilance data base (accessed 13.7.2021) 26 reports related to the intake of *Rhodiola rosea* are contained, 6 of them refer to the intake of Rhodiola products alone (no concomitant medication). The adverse events are related primarily to nervous system disorders (headache, nervousness, insomnia, dizziness) and gastrointestinal disorders (nausea, vomiting). No new safety issues could be identified from these reports. Regarding potential pharmacokinetic interactions see section 5.5.4.

In the SmPC section 4.8 'Undesirable effects' of registered medicinal products containing the herbal preparation as in the EU herbal monograph, nervous systems disorders (headache), gastrointestinal disorders (nausea, abdominal pain, diarrhoea) and hypersensitivity reactions (skin rash, itching) are listed.

Assessor's comment:

In the publications of clinical trials, a significant number of adverse events have been reported, but the level of detail is in most publications kept at the MedDRA system organ class (SOC) only. Mainly adverse events related to the SOCs gastrointestinal disorders and nervous system disorders have been reported. The few reports contained in the EudraVigilance data base refer to the same SOC.

In order to consider regulatory practice as well as the reports from clinical trials and from EudraVigilance, the following information is included to the monograph section 4.8 'Undesirable effects':

Nervous system disorders: Headache, nervousness, insomnia, dizziness. The frequency is not known.

Gastrointestinal disorders: Nausea, vomiting. The frequency is not known.

Skin and subcutaneous tissue disorders: Skin rash, itching. The frequency is not known.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

Although the use of registered traditional herbal medicinal products containing Rhodiola extract is permitted in adolescents, this age group cannot be considered in the monograph since no safety data from clinical trials in adolescents are available.

5.5.2. Contraindication

Hypersensitivity to the active substance is a contraindication in the monograph.

5.5.3. Special warnings and precautions for use

The standard statement that if the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted, is included in the monograph section 4.4.

5.5.4. Drug interactions and other forms of interaction

Reports of possible interactions in the Eudravigilance data base (accessed 13.7.2021) related to the concomitant use of *Rhodiola rosea* products together with one other drug substance refer to:

Sertraline: 1 case agitation, insomnia and memory impairment
Etanercept: 1 case dizziness, dysarthria and feeling drunk
Paroxetine: 1 case apallic syndrome, restlessness, serotonine syndrome and tremor; 1 case nausea, suicidal ideation, tremor
Duloxetine: 1 case dysphagia and oropharyngeal pain
Amitriptyline: 1 case somnolescence
Reports from concomitant use of more drugs cannot be related to Rhodiola.

Woron J & Siwek M (2018) report the analysis of 147 cases of adverse events of combinations of herbal medicinal products with (mostly psychotropic) pharmacotherapy. For Rhodiola (no data regarding type of herbal preparation, posology, duration of use) in combination with the below mentioned antidepressants the following symptoms of interactions were found:

Escitalopram: 1 case myalgia and ventricular arrhythmia
Escitalopram + trazodone: 1 case gum pain
Fluoxetine + mirtazapine: 2 cases qualitative disturbance of consciousness, restless legs syndrome
Paroxetine: 2 cases headache, joint pain
Duloxetine: 1 case acute throat pain and swallowing disorders
Duloxetine + sertraline: 1 case diarrhoea, jaundice and hepatotoxicity
Haloperidol: 1 case myoclonus, hypoglycaemia and sedation
Haloperidol + olanzapine: 1 case excessive sedation
Quetiapine + sulpiride: 1 case priapism
Risperidone: 3 cases catatonia, arthralgia, nausea and diarrhoea
Diazepam: 3 cases excessive sedation, hallucination and dizziness
Alprazolam: 1 case salivation and hypotension
Clonazepam: 1 case hyperhidrosis

Thu *et al*. (2016a) evaluated the effect of a Rhodiola dry extract (extract SHR-5, DER 2.5-5:1, first extraction solvent ethanol 70%, second extraction solvent water) on the activity of the CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. 13 healthy volunteers received as probe drugs caffeine (CYP1A2), losartan (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6 and midazolam (CYP3A4) with and without 14 days pre-treatment with 290 mg Rhodiola extract. A 21% decreased ratio of the active metabolite EXP-3174 to the parent drug losartan was found, indicating a reduced CYP2C9 metabolic activity.

Maniscalco *et al*. (2015) report a case of a possible interaction due to the concomitant use of paroxetine and a product containing *Rhodiola rosea* (no details regarding herbal preparation, dosage of 400 mg per day). The patient (68 years old, since the age of 24 diagnosed with recurrent moderate depression) received paroxetine (20 mg per day) and started to take the Rhodiola product. After 15 days the patient developed a vegetative syndrome, restlessness and trembling. The authors interpret the symptoms as a serotonergic syndrome. The authors exclude pharmacokinetic interactions. A possible explanation is seen by the authors by the inhibition of CYP2D6 by paroxetine and as a consequence an overdose of Rhodiola.

Assessor's comment:

A 21 % decrease in the EXP-3174/losartan ratio at four hours after dosing was found in one study (Thu et al., 2016a) after two weeks pretreatment with R. rosea, indicating a reduced CYP2C9 metabolic

activity. The clinical relevance is unclear. Relevant interactions have not been reported from post-marketing experience and do not pose a risk based on current knowledge.

The following information is included in the monograph section 4.5: "No clinically relevant interactions have been observed."

5.5.5. Fertility, pregnancy and lactation:

No data published. The safety during pregnancy and lactation has not been established. In the absence of data the use during pregnancy and lactation is not recommended.

5.5.6. Overdose

There are no case reports published.

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

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

5.5.8. Safety in other special situations

Not applicable.

5.6. Overall conclusions on clinical safety

Adverse events, mainly non-serous and related to the SOCs nervous system disorders, gastrointestinal disorders and skin and subcutaneous tissue disorders have been reported. The use in children and adolescents as well as during pregnancy and lactation cannot be recommended. Based on the published data it can be concluded that traditional herbal medicinal products containing *Rhodiola rosea* are not harmful when used in the specified conditions.

6. Overall conclusions

Herbal preparations of the underground organs of *Rhodiola rosea* are used in traditional medicine since centuries. Dry extracts (DER 1.5-5:1), extraction solvent ethanol 67-70% V/V, are in medicinal use within the European Union since 1987. Therefore the criteria for 30 years of medicinal use as defined for traditional herbal medicinal products in Directive 2004/24 are fulfilled. The traditional use as an adaptogen for the relief of symptoms of stress such as fatigue and exhaustion is appropriate for traditional herbal medicinal products.

The published clinical trials exhibit considerable deficiencies in their quality. Therefore 'well-established use' cannot be accepted.

The clinical trials as well as the traditional use do not give reasons for special safety concerns. No serious adverse events are reported.

Due to the missing published data on genotoxicity the development of a European Union List Entry cannot be supported.

Annex

List of references