Rosenroot (Rhodiola rosea): Traditional use, chemical composition, pharmacology and clinical efficacy

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Review Article

Rosenroot (*Rhodiola rosea*): Traditional use, chemical composition, pharmacology and clinical efficacy

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ABSTRACT

The aim of this review article was to summarize accumulated information related to chemical composition, pharmacological activity, traditional and official use of *Rhodiola rosea* L. in medicine. In total approximately 140 compounds were isolated from roots and rhizome - monoterpene alcohols and their glycosides, cyanogenic glycosides, aryl glycosides, phenylethanoids, phenylpropanoids and their glycosides, flavonoids, flavonlignans, proanthocyanidins and gallic acid derivatives. Studies on isolated organs, tissues, cells and enzymes have revealed that Rhodiola preparations exhibit adaptogenic effect including, neuroprotective, cardioprotectiv e, anti-fatigue, antidepressive, anxiolytic, nootropic, life-span increasing effects and CNS stimulating activity. A number of clinical trials demonstrate that repeated administration of *R. rosea* extract SHR-5 exerts an anti-fatigue effect that increases mental performance (particularly the ability to concentrate in healthy subjects), and reduces burnout in patients with fatigue syndrome. Encouraging results exist for the use of Rhodiola in mild to moderate depression, and generalized anxiety. Several mechanisms of action possibly contributing to the clinical effect have been identified for Rhodiola extracts. They include interactions with HPA-system (cortisol-reducing), protein kinases p-JNK, nitric oxide, and defense mechanism proteins (e.g. heat shock proteins Hsp 70 and FoxO/DAF-16). Lack of interaction with other drugs and adverse effects in the course of clinical trials make it potentially attractive for use as a safe medication. In conclusion, *Rhodiola rosea* has robust traditional and pharmacological evidence of use in fatigue, and emerging evidence supporting cognition and mood.

Contents

Introduction

Recently, a narrative review article entitled "Perspective on Roseroot (*Rhodiola rosea*) studies" by Blomkvist, Taube and Larhammar, was published online 2009, May 25, *Planta Medica* (Blomkvist et al., 2009), where the performance of statistical analyses of several selected clinical trials on Rhodiola were criticized for purported methodological weaknesses. In the conclusion the focus on the paper was primarily on finding failings of the studies without any systematic assessment of the level of scientific evidences of the efficacy of *Rhodiola rosea* (Rhodiola).

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The aim of this review article is to systematically assess Rhodiola clinical trials in accordance with existing standards and guidelines of EMEA and Natural Standards. This is in order to estimate the level of scientific evidences of efficacy and grade of recommendations for use of the plant in the treatment of specific conditions (e.g. fatigue, depression). In addition to a review of clinical efficacy, an overview of the traditional use, and a comprehensive analysis of the adaptogenic mechanisms of action by Rhodiola's constituents are outlined.

Traditional and Current Medical Use of Rhodiola

Rhodiola rosea L. (Crassulaceae, syn. *Sedum rhodiola* - DC. *Sedum rosea* - (L.) Scop cop, is known by the common names Rhodiola, Roseroot, Rosenroot, Golden Root, Arctic Root, Orpin Rose, Rhodiole Rougeâtre), and has a long history as a valuable medicinal plant having appeared in the Materia Medica of a number of European countries (Linné, 1749; Sparschuch, 1775; Pharmacopée Française, 1976; Virey, 1811). The plant grows in crevices of mountain rocks and on sea cliffs of Arctic regions of Europe, Asia (mainly in Siberia) and N. America, including Britain, further south on mountains. The main source of commercially available roots and rhizome are Mountain Altai and in south region of foothill Altai, mainly in Ust-Kanski, Ust-Koksinski, Charishki regions (Saratikov and Krasnov, 2004). In all, there are approximately 24 different species of genus Rhodiola including eight species containing phenolic compounds and growing in Altay region that can be mis-identified with *Rhodiola rosea* L (Kurkin et al., 1985a, 1985b; Kurkin and Zapesochnaya, 1986a).

According to some sources, *Rhodiola rosea* was in use as far back as the Vikings as a medicine and for its strengthening action on hard work (Magnusson, 1992; Dragland and Galambosi, 1996), but this is somewhat speculative. In Linnés *Materia medica* (Linné, 1749) the root of the rose is recommended in the treatment of headaches, "hysteria", hernias, discharges, and as an astringent. The use of the root is also found in the first Swedish national pharmacopoeia (Sparschuch, 1775). In an old book of useful plants from Iceland (Halldorsson, 1783) the following statement about Rhodiola is written - "Infusion of stone crop taken dries and astringes, heals pain in the mouth, heals kidneys from sand which forms stones, stops diarrhea and cures headache and also strengthens head and also hair growth in the head is washed with it. The root may also be suitable for severe skin conditions. Grinded, pressed and mixed with butter it is considered to relieve swellings and decreases back pain and pains in joins and other painful conditions, especially if heat is applied. The dried root has been used to cures swellings, removes freckles and is strengthening for the head" (Halldorsson, 1783). It is also seen to "enhance the intellect", "tonic against infirmity" and "restores weak nerves" (Halldorsson, 1783). Alm (Alm, 2004) mentioned the use of Rhodiola in folk medicine against scurvy, being also medically used as a stimulant and an astrigent in France (as described by Virey in a medicine textbook in 1811). The recent use of the herbal medicine in traditional medicine in Sweden is reported in northern Jämtland. During interviews with Lapps it has been mentioned that they chewed on bits of roots during long journeys (Magnusson, 1992; Dragland, 2001). It is also said to have been used against headaches and when washing hair.

In the textbook of pharmacology for dispenser training in Sweden, *Rhodiola rosea* is mentioned as a plant with a stimulant effect. It is further ascribed the vasoconstrictive and haemostatic effects on haemorrhoids (Sandberg and Bohlin, 1993). Also in the Pharmaceutical Book (Läkemedelsboken) 97/98 *Rhodiola rosea* is mentioned as one of the more common herbal medicines and its

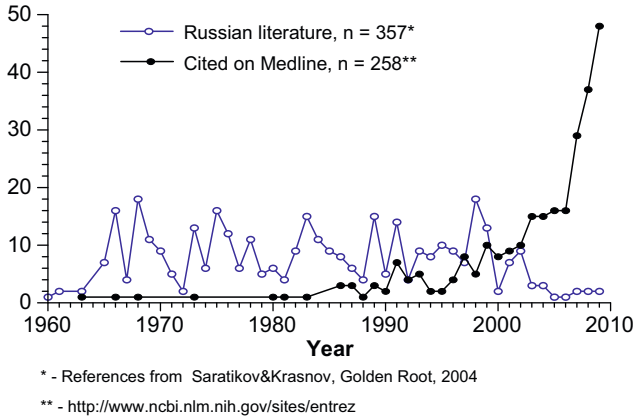

Fig. 1. demonstrates increasing interest to this plant in scientific community. In total about 600 scientific publication on *Rhodiola rosea* can be found in the literature.

effect is specified as a "general strengthener" and "psychostimulantium" (Strandberg and Aly, 1997).

Preparations of the drug now form part of the official medicine of some of various countries (Müller-Dietz, 1969; Mashkovskij, 1977; Muravijeva, 1978; Turova and Sapozhnikova, 1984; National Pharmacopoeia of the USSR, 1990; National Pharmacopoeia Committee, 1996; Estonian Ministry of Health Affairs, 1998). *Rhodiola rosea* is one of the most popular plant adaptogens utilized in Russia today, and has been published on extensively (Fig. 1). It was first recommended in 1969 by the Pharmacological Committee of the Ministry of Health of the USSR for use as a stimulant against fatigue by patients who suffered asthenic states and by healthy people who showed astheny during periods of high mental exertion or after intensive physical work. The drug can also be applied in cases of borderline nervous-mental diseases, neuroses, neurotic disorders and psychopathies. In psychiatric practice, extracts of *Rhodiola rosea* are indicated for the correction of neurological side-effects associated with psychopharmacological therapy, and for the intensification and stabilization of remissions of asthenic and apathistical-aboulic type schizophrenia patients (Saratikov et al., 1965; Krasik et al., 1970a, b; Saratikov, 1973; Komar et al., 1981; Mikhailova, 1983; Brichenko et al., 1986; Saratikov and Krasnow, 1987).

As a dietary supplement, numerous preparations of Rhodiola extracts are used world-wide (Khanum et al., 2005). The functional claim of Rhodiola dietary supplements currently mentioned in the Consolidated list of Article 13 health claims of the European Food Safety Authority (EFSA) is formulated as following – "contributes to optimal mental and cognitive activity" [http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_article13.htm]

In Sweden Rhodiola tablets containing *Rhodiola rosea* SHR-5 extract have been on the market since 1985 . They are currently registered as Traditional Herbal medicinal product (THMP) indicated as an adaptogen (Box 1) in situations of decreased performance such as fatigue and sensation of weakness.

Chemical composition

Rhodiola rhizomes contains essential oils, fats, waxes, sterols, glycosides, organic acids (oxalic, citric, malic, gallic, succinic), phenolics including tannins and proteins (Zapesochnaya and Kurkin, 1983; Zapesochnaya and Kurkin, 1982; Kurkin et al., 1985a; Kurkin and Zapesochnaya, 1986a, b; Rohloff, 2002; Tolonen et al., 2003; Saratikov and Krasnov, 2004; Akgul et al., 2004; Ma et al., 2006; Yousef et al., 2006; Ali et al., 2008).

Box 1–Adaptogenic definitions

Adaptogens comprise a pharmacotherapeutic group of herbal preparations used to:

- increase attention and endurance in fatigue, and
- prevent/mitigate/reduce stress-induced impairments and disorders related to neuro-endocrine and immune systems [Panossian and Wikman, 2009a, b].

Other definition of adaptogens are associated with physiological conditions:
Adaptogenic substances are stated to have the capacity to normalize body functions and strengthen systems compromised by stress. They are reported to have a protective effect on health against a wide veriety of environmental assults and emotional conditions EMEA/HMPC/102655/2007,
Adaptogens are compounds which could increase ''the state of non-specific resistance'' in stress [Lazarev, 1958; Lazarev et al., 1959]
Adaptogens are innocuous agents, nonspecifically increasing resistance against physically, chemically, biologically and psychologically noxious factors (''stressors''), normalizing effect independent of the nature of pathologic state [Brekhman and Dardymov, 1968].
Adaptogens are substances which elicit in an organism a state of non-specifically raised resistance allowing them to counteract stressor signals and to adapt to exceptional strain [Wagner et al., 1994].

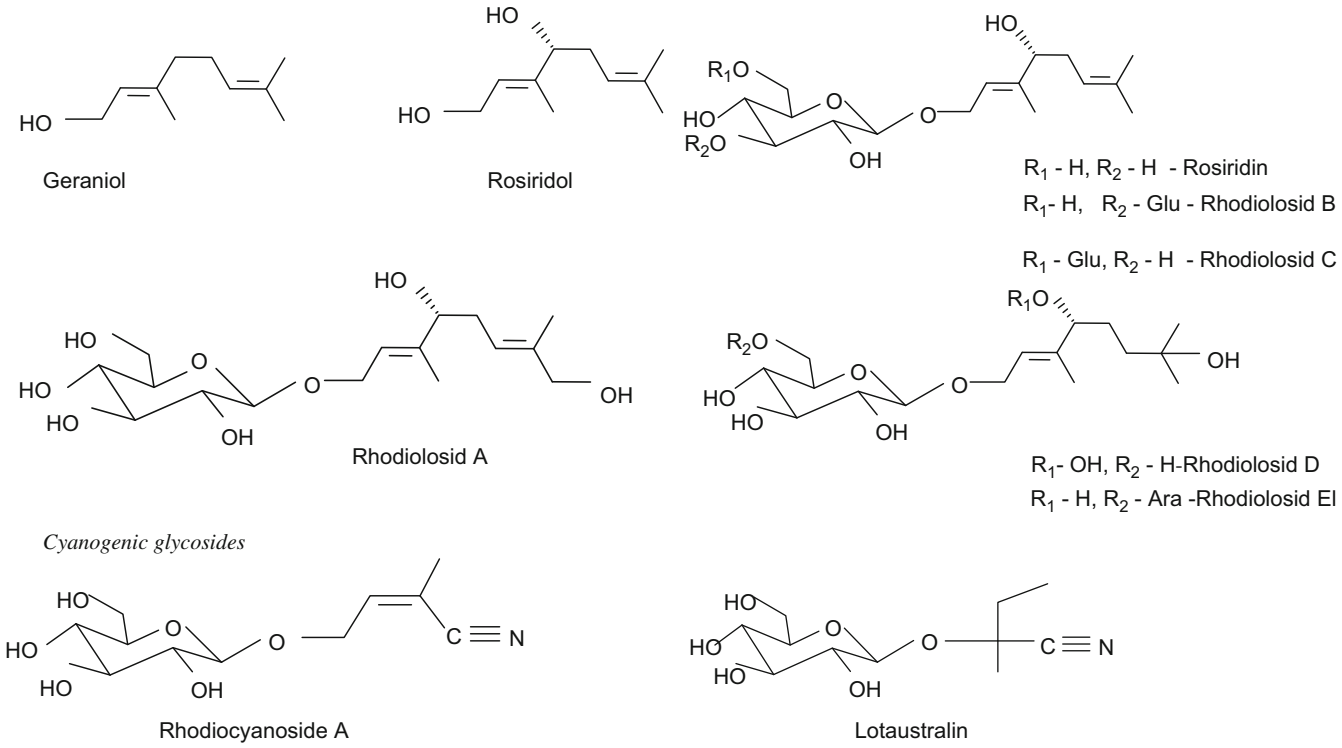

Fig. 2. Monoterpene alcohols and their glycosides.

The dried rhizomes contained 0.05% essential oil with the main chemical classes: monoterpene hydrocarbons (25.40%), monoterpene alcohols (23.61%) and straight chain aliphatic alcohols (37.54%). n-Decanol (30.38%), geraniol (12.49%) and 1,4-p-menthadien-7-ol (5.10%) were the most abundant volatiles detected in the essential oil, and a total of 86 compounds were identified (Rohloff, 2002). Geraniol was identified as the most important rose-like odor compound besides geranyl formate, geranyl acetate, benzyl alcohol and phenylethyl alcohol. Its oxygenated metabolite Rosiridol is an aglycon of Rosiridin (Kurkin et al., 1985a; Kurkin and Zapesochnaya, 1986b) - one of the most active constituents of Rhodiola in bioassay guided fractionation of Rhodiolathe extract (van Diermen et al., 2009). Rosiridin was found to inhibit monoamine oxidases A and B *in vitro* implying its potential beneficial effect in depression and senile dementia (van Diermen, 2009).

More than 50 polar compounds were isolated from the water alcoholic extracts, they are

monoterpene alcohols, their glycosides and cyanogenic glycosides (Fig. 2). In Fig. 3 are listed phyhylethanoids, phenylpropanoids, flavonoids, aryl glycosides, proanthocyanidins and other gallic acid derivatives. (Zapesochnaya and Kurkin, 1983, 1983; Kurkin et al., 1985a; Kurkin and Zapesochnaya, 1986a, b; Ganzera et al., 2001; Tolonen et al., 2003; Saratikov and Krasnov, 2004; Akgul et al., 2004; Ma et al.2006, Yousef et al., 2006, Ali et al.,2008; Avula et al., 2009).

Biologically active compounds include phenolic and/or cyanogenic glycosides with antidepressive, anti-fatigue, cognitive-enhancing, anti-anoxia, hepatoprotective, anti-allergy, anti-inflammatory,

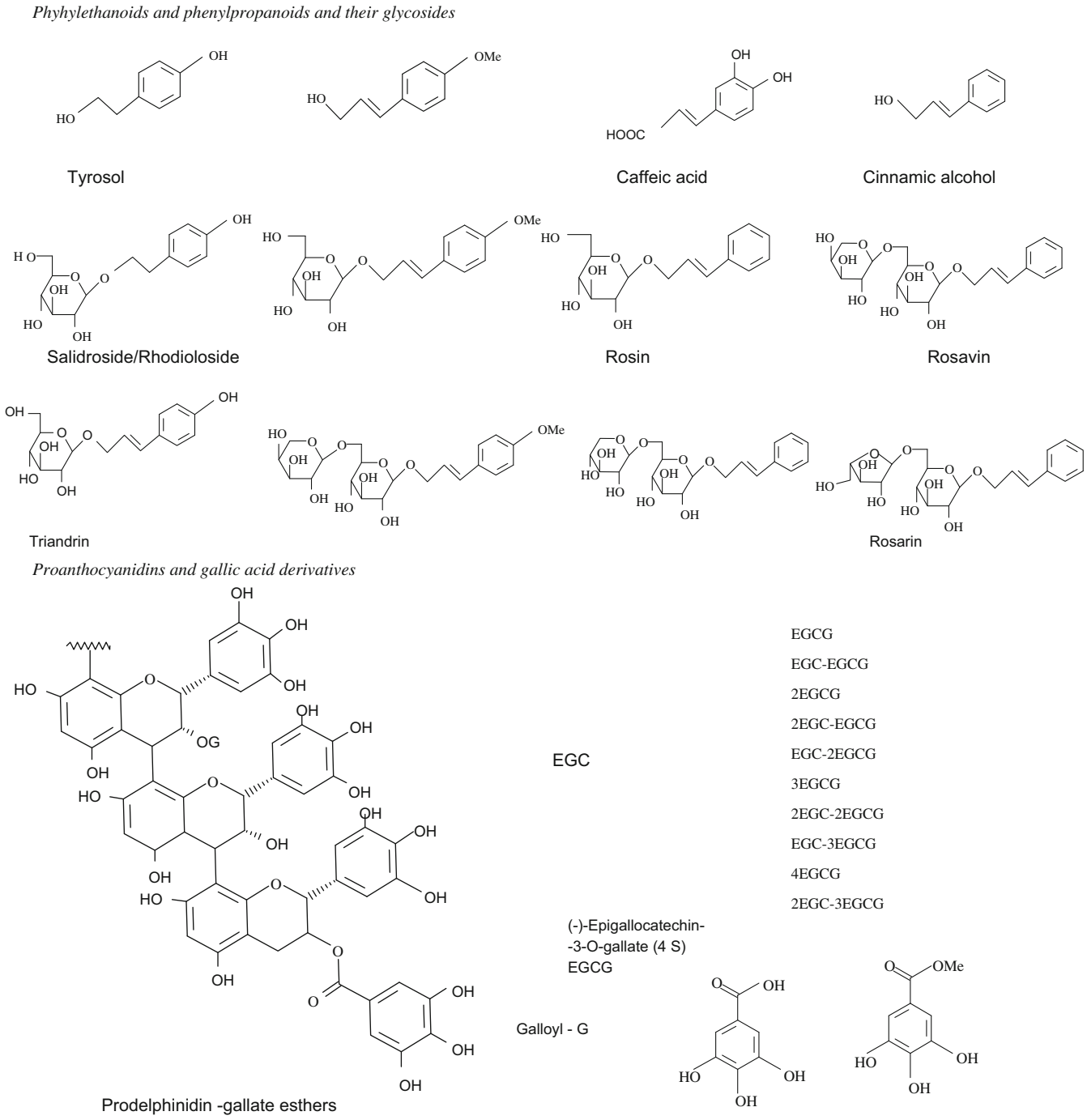

Fig. 3. Phyhylethanoids, phenylpropanoids and their glycosides, proanthocyanidins and gallic acid derivatives, flavolignans, aryl glycosides and flavonoids.

properties (Kurkin, and Zapesochnaya, 1986a; Panossian et al., 2008a; van Diermen et al., 2009; Diaz-Lanza et al., 2001). The constituent with known therapeutic activity was found is *p*-hydroxyphenylethyl-*O*-ß-D-glucopyranoside (*Syn.*salidroside, rhodioloside, rhodosin) (Aksenova et al., 1968).

Proanthocyanidins constituting a fairly large portion of the Rhodiola extracts (ca. 30% of the 70% acetone dry crude extract) (Yousef et al., 2006), were also noted for significant bioactivities including antioxidant, anti-cancer, anti-inflammatory, anti-allergic, anti-mutation, anti-aging and improving liver function (Yousef et al., 2006). The MAO-B inhibitory activity of EGCG has been described by van Diermen et al., 2009, however this effect is attributed rather to its denaturant effect on proteins than to a specific mechanism of inhibition (van Diermen et al., 2009).

The phytochemical constituents in Rhodiola are species-dependent (Kurkin et al., 1985a, b, 1986; Kurkin and Zapesochnaya, 1986a; Yousef et al., 2006), although salidroside production in other species including *R. quadrifida (Pall.)* Fisch and Mey, *R algila(Ledeb.)* Fisch *R. sachalinensis, R. kirilowii*, *R. crenulata R. heterodonta* and *R. semenovii* has also been reported (Kurkin and Zapesochnaya, 1986a, b; Saratikov and Krasnov, 2004; Wu et al., 2003; Yousef et al., 2006; van Diermen et al., 2009). Characteristic feature of *R. rosea* is presence of cynnamic alcohol glucosides and relatively high content of phenylpropanoids rosavin, which was not detected in other 21

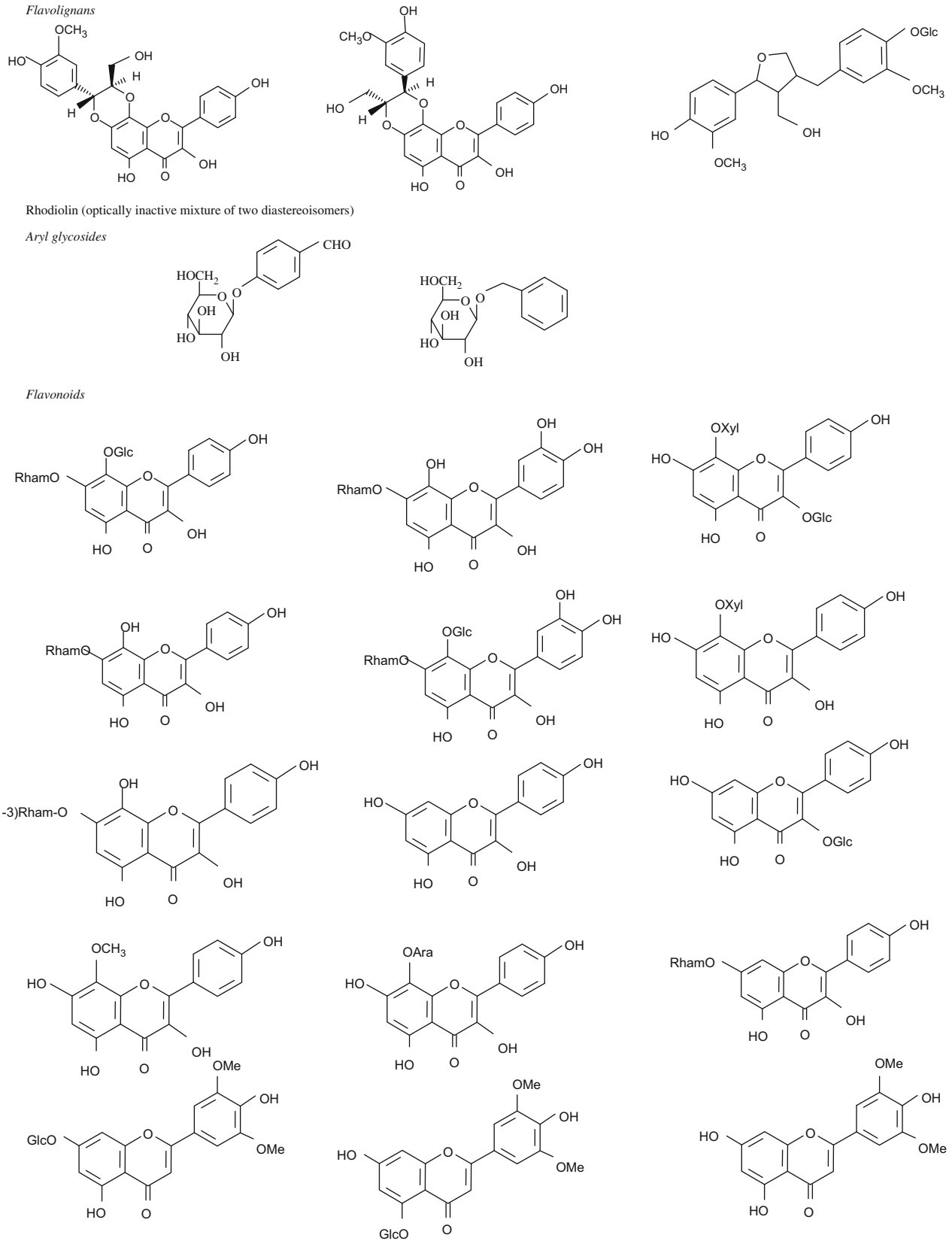

Fig. 3. (*Continued*)

genus Rhodiola species morphologically similar to *R. rosea* (Kurkin et al., 1985a, b, 1986; Kurkin and Zapesochnaya, 1986a; Yousef et al., 2006). Commercial preparations based on *R. rosea* must be free of morphologically similar *R. quadrifida (Pall.)* Fisch and Mey, *R algila(Ledeb.)* Fisch and Mey, and other foreign plant materials. Typical HPLC fingerprint is shown on the Fig. 4.

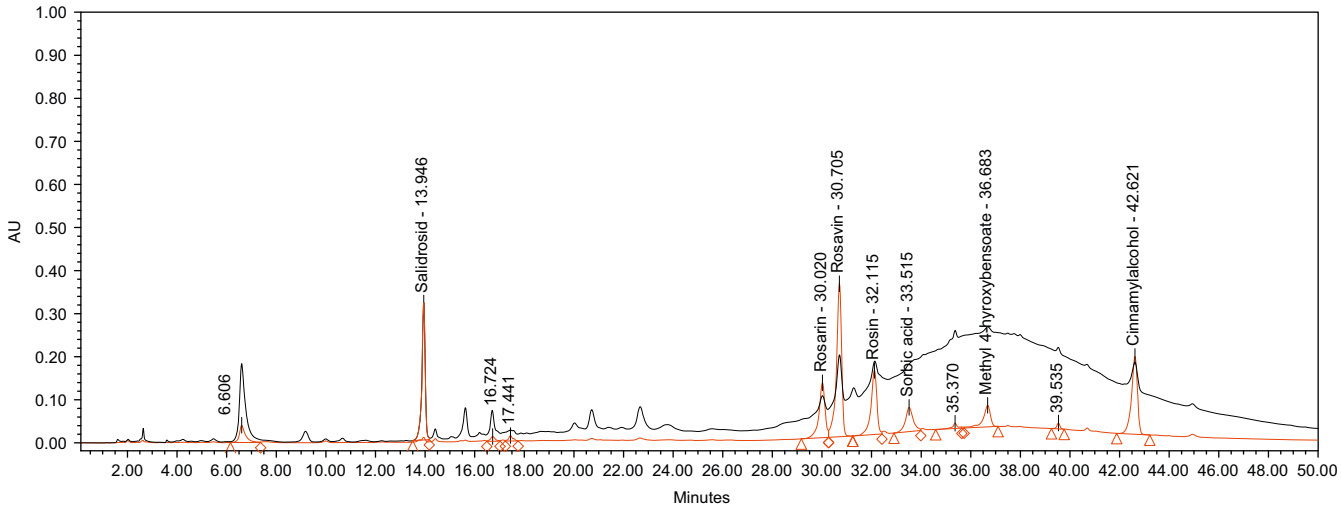

Fig. 4. HPLC fingerprints overlay from *Rhodiola rosea* L. roots extract (DER_{native} 2,5-5.0 :1, extraction solvent 70% ethanol) containing 2.7% salidroside, 6.0% rosavin and 0.8% tyrosol, detected at 221 nm (black line, peak of Salidroside is in red color) and 252 nm (red line) by photodiode array detector (Waters model 996). The HPLC column packed with octadecyl silica (LiChrospher RP-18) was eluted with the solvent system containing gradually increasing concentration (from 5 to 95%) of acetonitrile in water solution of 0.001 M ortho phosphoric acid. Broad band of background absorption with max at 270-275 nm from 28 min to 50 min is due to unresolved epigallcatechingallate oligomers. Sorbic acid and methylboezoate – preservatives added to the extract.

Various new methods of analysis of active constituents in the extracts of herbal substance, herbal preparations and biological fluids were developed during last decade (Avula et al., 2009; Chang et al., 2007; Ganzera et al., 2001; Mao et al., 2007a; Mao et al., 2007b; Peng et al., 2008 ; Petsalo et al., 2006; Tolonen and Uusitalo, 2004; Wiedenfeld et al., 2007; Wu et al., 2004).

Pharmacological activity and mechanisms of action

Results of more than few hundred pharmacological studies of *Rhodiola rosea* are reviewed in several review articles and books (Saratikov et al., 1968; Saratikov, 1976; Saratikov and Krasnov, 2004; Panossian and Wagner, 2005; Brown et al., 2002; Kelly, 2001; Panossian, 2003; Panossian and Wikman, 2005, 2009a; Panossian and Wagner, 2005).

Pharmacological effects of *Rhodiola rosea* extracts described in these studies are summarized below:

- Adaptogenic and stress- protective (neuro-cardio and hepato-protective) effects
- Cardioprotective effects
- Antioxidant effect
- Stimulating effect on the central nervous system including effects on cognitive functions such as attention, memory and learning
- Anti-fatigue effect
- Antidepressive and anxiolytic effects
- Endocrine activity normalizing
- Life-span increasing effect

Stress-protective effect of Rhodiola, that increased survival of simple organisms and isolated cells in oxidative stress is not purely associated with its antioxidant or pro-oxidant effects (Schriner et al., 2009; Wiegant et al., 2008, 2009), because the ability of Rhodiola to enhance survival against oxidative stress at dose levels that do not elevate the major antioxidant defenses, activate the antioxidant response element or degrade H_2O_2 (Schriner et al., 2009).

The adaptogenic effect of Rhodiola root SHR-5 extract have been shown in several double blind, randomized controlled clinical trials, Table 3. Orally administrated for 2-6 weeks dry SHR-5 extract prepared with ethanol-water (ethanol 70% (V/V) in the daily doses of 288 – 680 mg (1-4 tablets), have been shown to improve mood (Darbinyan et al., 2007), cognitive performance, attention (Olsson et al., 2009; Darbinyan et al., 2000; Shevtsov et al., 2003; Spasov et al., 2000) and relief fatigue (Olsson et al., 2009; Darbinyan et al., 2000; Shevtsov et al., 2003; Spasov et al., 2000; Schutgens et al., 2009) in stress related conditions. A single dose effect is achieved in one-two hours after the administration of Rhodiola extracts (Perfumi and Mattioli, 2007; Mattioli and Perfumi, 2007; Panossian et al., 2009b; Mattioli et al., 2008; Panossian et al., 2009a).

The adaptogenic effect of Rhodiola root water-acloholic extracts have been confirmed in many preclinical studies (Saratikov, 1976; Saratikov et al., 1968; Aksenova et al., 1968; Panossian and Wagner, 2005; Jafari et al., 2007; Perfumi and Mattioli, 2007; Mattioli et al., 2008; van Diermen et al., 2009; Abidov et al., 2003; Iaremiĭ and Grigor'eva, 2002; Qin et al., 2008; Siwicki et al., 2007; Wang et al., 2009; Pooja et al., 2009; Zdanowska et al., 2009) and several controlled clinical trials (Aksenova et al., 1968a,b; Dieamantet al., 2008; Bystritsky et al., 2008; Earnest et al., 2004; Xu et al., 2003; Ha et al., 2002; Zhang et al., 1999; Fintelmann and Gruenwald, 2007; Spasov et al., 2000; Bocharova et al., 1995).

In numerous *in vitro* and *in vivo* studies on animals, CNS stimulating (Saratikov, 1976; Sokolov et al., 1985, 1990; Barnaulov et al., 1986; Saratikov et al., 1968; 1978a, b; Aksenova et al., 1968a, b; Kurkin et al., 2003; Panossian and Wagner, 2005; Perfumi and Mattioli, 2007 ; Mattioli et al., 2008; Qin et al., 2008), neuro-,cardio- and hepato-protective effects (Wang et al., 2008; Iaremiĭ and Grigor'eva, 2002; Saratikov and Krasnov, 2004), life-span increasing (Jafari et al., 2007; Wiegant et al., 2009), MOA inhibitory (van Diermen et al., 2009), immunotropic (Siwicki et al., 2007), antiviral (Wang et al., 2009), anti-inflammatory (Pooja et al., 2009) and antibacterial activity (Zdanowska et al., 2009) has been demonstrated.

Using animal models, bioassay-guided fractionation of various extracts of plant adaptogens have shown that the active principles are mainly phenylpropane and phenylethane derivatives including salidroside, rosavin, syringin, triandrin, tyrosol, etc. (Aksyonova, 1968; Kurkin and Zapesochnaya, 1986a; Zapesochnaya et al., 1995; Barnaulov et al., 1986; Sokolov et al., 1990; Saratikov and Krasnov, 2004). Of these, rhodioloside/salidroside and triandrin was reported to be the most active in a number

Table 1
Randomized and non-randomized clinical trials of Rhodiola in mental fatigue, stress-induced fatigue, fatigue syndrome and asthenia.

Adaptogen (active principle)	Indication for use and/or pharmacological activity	Number of trials	Number of subjects	Grade of recommendation	
				EMEA[a]	NSR[b]
Rhodiola rosea	**Mental fatigue**: Rhodiola can improve attention in cognitive function in fatigue after single and repeated administration.	3	257	A	A
	Fatigue syndrome: Rhodiola has anti-fatigue effect in physical, emotional, and mental exhaustion.	1	60	A	B
	Mild depression: Rhodiola has an anti-depressive effect	1	89	A	B
	Stimulating effect: Rhodiola can improve mental performance after single dose administration	3	419	B	B
(Rhodioloside)	**Stimulating effect**: Rhodioloside can improve mental performance after single dose administration	1	46	B	

[a] Grade of recommendation based on the European Medicines Agency Assessment Scale [EMEA/HMPC/104613/2005]:

Grade A. Evidence levels quality Ia, Ib - Requires at least one randomized controlled trial as part of the body of literature of overall good consistency addressing the specific recommendation;
Grade B. Evidence levels IIa, IIb, III - Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation;
Grade C. Evidence level IV - Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities but indicates absence of directly applicable studies of good quality.

[b] Grade of recommendation according to Natural Standards Evidence-Based Validated Grading Rationale (Basch and Ulblicht, 2005):

Grade A. Strong scientific evidence - Statistically significant evidence derived from: (i) more than two properly conducted randomized controlled trials (RCT), or (ii) one properly conducted randomized controlled trial, and one properly conducted meta-analysis, or (iii) multiple RCTs with a clear majority of the properly conducted trials and with supporting evidence in basic science, animal studies or theory;
Grade B. Good scientific evidence - Statistically significant evidence derived from: (i) one or two properly conducted randomized trials, or (ii) one or more properly conducted meta-analysis, or (iii) more than one cohort/case control/non-randomized trials and with supporting evidence in basic science, animal studies or theory;
Grade C. Unclear or conflicting scientific evidence - Evidence derived from: (i) one or more small RCT without adequate size, power, statistical significance, or quality design by objective criteria, or (ii) conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, or (iii) more than one cohort/case control/non-randomized trial *and* without supporting evidence in basic science, animal studies or theory, *or* evidence of efficacy only from basic science, animal studies or theory

of different test systems (Barnaulov et al., 1986; Sokolov et al., 1990).

Rhodioloside and salidroside - active principles of the SHR-5 extract, were found to have neuro-cardio-and hepato- protective activity preventing/mitigating/reducing stress-induced impairments and disorders related to neuro-endocrine and immune systems by:

- Protection from oxidative damage in fatigue (Ma et al., 2009)
- Protection of liver tissue from the acetaminophen -induced oxidative damage via preventing or alleviating intracellular GSH depletion and oxidation damage, which suggested that it would be a potential antidote against APAP-induced hepatotoxicity (Wu et al., 2008)
- Inhibition of lipid peroxidation and oxidative stress in rat hepatic stellate cells (Zhang and Liu, 2005)
- Hepatoprotection against tacrine-induced cytotoxicity in human liver-derived Hep G2 cells (Song et al., 2003)
- Promotion of the recovery of hematopoietic function of the bone marrow depressed anemia (Zhang et al., 2005; 2006)
- Stimulation of CNS system (Saratikov et al., 1968; Aksenova et al., 1968; Panossian and Wagner, 2005; Saratikov and Krasnov, 2004)
- Reduction of the degree of cerebral edema of rats with global cerebral ischemia-reperfusion injury, relieving the metabolism abnormity of free radical and improving the function of cognition (Zou et al., 2009)
- Blockage of H(2)O(2)-induced apoptosis in rat neuronal PCl2 cells (Cai et al., 2008)
- Attenuation of glutamate-induced apoptotic cell death in primary cultured hippocampal neurons of rats (Chen et al., 2008)
- Protection of the cultured neuronal cell PC12 cells against hypoglycemia 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 (Yu et al., 2008)
- Protection of cultured neuronal cells from sodium azide and glutamate induced injuries (Cao et al., 2005, 2006)
- The effect of anti-neuronal apoptosis relating to its function of decreasing intracellular free calcium concentration (Zhang et al., 2004; 2007)
- Protection rat neuronal PCl2 cells against amyloid beta-peptide (Abeta)-induced cytotoxicity reducing accumulation of reactive oxygen species and malondialdehyde (MDA) (Jang et al., 2003)
- Protection of cultured myocardial cells from anoxia and reoxygenation induced injuries of cell membrane, endoplasmic reticulum, and mitochondria (Ye et al., 1993)
- Protection of cardiomyocytes against hypoxia-induced necrosis and apoptosis (Zhang et al., 2009)
- Significant inhibition of tumour – induced neovascular reactions (Skopńska-Rózewska et al., 2008)
- Normalizing effect on elevated or reduced glucose level in blood of stressed-animals (Saratikov et al., 1968)
- Promotion of the 3H-glucose uptake, suppresses the differentiation and down-regulates the expression of PPAR-gamma and C/EBP-alpha mRNA in 3T3-L1 adipocytes (Wang et al., 2004)
- Stimulation of glucose uptake in skeletal muscle cells by activating phosphorilation of AMP-activated protein kinase (Li et al., 2008)
- Antiviral effect against cultured CVB3 cells, indication on a potential effect in viral myocarditis (Wang et al., 2008)

Some of these findings might raise a possibility of potential therapeutic applications of salidroside for preventing and treating cerebral ischemic and neurodegenerative diseases (Yu et al., 2008). Salidroside can be further developed as potential compound for the anti-diabetic therapy (Li et al., 2008).

Several mechanisms of action possibly contributing to the clinical effect have been identified for whole SHR-5 extract both in

Table 2
Results of non-randomized studies on humans involving effects of Rhodiola on mental performance in fatigue.

Type of preparation tested in the study	Study design[a]	Number of subjects in the study	Age range of subjects	Daily dose	Duration of study	Effects recorded	Classification of evidence level[b]	Ref.
Salidroside	PC, SB	46	20-28	2.5 mg	acute	Improved mental performance; reduced the number of errors in Anfimov's correction test; stimulating effect lasting 4 h or more.	IIa	Aksenova, 1968
Rhodiola rosea (extract)	PC, SB	80 healthy students (control group) and 70 patients with neurosis	?	10 drops or 3x10 drops/ day	acute and 10 days	Single and repeated administration of adaptogens improved functional state of the CNS in patients with neurosis as characterized by normalization of the speed and power of neural processes in Ivanov-Smolenski's verbal test with speech-supported locomotor-conditioned reflex measurement. The memory improved and attention became more stable.	IIa	Kaliko and Tarasova (1966)
Rhaponticum cartamoides (extract)			20-50	40 drops or 3x10 drops/ day				
Rhodiola rosea (40% ethanol tincture)	PC	254	19-22	20 drops	acute	Improved mental performance; reduced the number of errors in Anfimov's correction test; increased the accuracy, working capacity and speed of information perception. Stimulating effect lasted 4 h or more.	IIa	Komar, 1981
E. senticosus (40% ethanol tincture)				20 drops				
Extract of *R. rosea* rhizome				0.3 g				
Tyrosol	?	82	?	1, 5, 10 and 20 mg	?	Improved mental performance, reduced the number of errors in Anfimov's correction test.	III	Marina et al. (1994)
R. rosea extract				5 drops				
R. rosea (tincture 40% ethanol)	PC	85	20-28	5-10 drops	acute	Improved mental performance, reduced the number of errors in Anfimov's correction test: the stimulating effect lasted 4 h or more	IIb	Zotova, 1965
R. rosea (extract in combination with vitamins and minerals)	C	120	50-89	2 capsules 1 capsule	12 weeks	Improved in cognitive deficiencies (concentration deficiencies, forgetfulness, decreased memory, susceptibility to stress, irritability)	III	Fintelmann, 2007

[a] CO - crossover; DB - double-blind; SB - single blind, NC - not controlled; PC - placebo-controlled; C – controlled.
[b] According to WHO, FDA and EMEA: Ia - meta-analyses of randomized and controlled studies; Ib - evidence from at least one randomized study with control ; IIa - evidence from at least one well-performed study with control group; IIb - evidence from at least one well-performed quasi-experimental study; III - evidence from well-performed non-experimental descriptive studies as well as comparative studies, correlation studies and case-studies; and IV - evidence from expert committee reports or appraisals and/or clinical experiences by prominent authorities.
[c] ? - data not listed or unavailable.

human (Olsson et al., 2009) and animal studies (Panossian and Wikman, 2009a; Panossian et al., 1999; 2007; 2008c; 2009a; Boon-Niermeijer et al., 2000; Wiegant et al., 2008, 2009) . They include interactions with HPA-system, particularly inhibition of stress induced secretion of cortisol (Olsson et al., 2009; Panossian et al., 2007; 2009a; Lishmanov et al., 1987), protein kinases p-JNK (Panossian et al., 2007; 2009a), nitric oxide (Panossian et al., 2007; 2009a), heat shock proteins Hsp 70 (Lishmanov et al., 1996; Prodius et al., 1997; Panossian et al., 2008c, 2009a; Wiegant et al., 2008) and expression of FoxO/DAF-16 proteins (Wiegant et al., 2009) proteins involved in defense mechanisms to cope with stress and stress-induced disorders.

It has been demonstrated that beneficial stress-protective activity of Rhodiola is associated with the hypothalamic-pituitary-adrenal axis and the regulation of key mediators of stress response including molecular chaperons (e.g. Hsp70) (Lishmanov et al., 1996; Prodius et al., 1997; Panossian et al., 2008c, 2009a; Wiegant et al., 2008), stress-activated c-Jun N-terminal protein kinase 1 (JNK1) (Panossian et al., 2007), Forkhead box O (FOXO) transcription factor DAF-16 (Wiegant et al., 2009), cortisol (Olsson et al., 2009; Panossian et al, 2007), nitric oxide (Panossian et al., 2007) and betta-endorphine (Lishmanov et al., 1987; Maslov et al., 1997; Maĭmeskulova et al., 1997). Anti-depressive effect of Rhodiola can be associated both by its effect on mono-amine oxidase A (van Diermen et al., 2009), and on stress-system, namely on secretion of cortisol (Darbinyan et al., 2007; Olsson et al., 2009) and JNK mediated effects on glucocorticoid receptors (Panossian et al., 2007).

Other possible mechanisms of action Rhodola extracts are not excluded, such as a possible effect on neuropeptide Y receptors (Larhammar and Salaneck, 2004) and expression of neuropeptide Y which is known play important role in regulation of energy balance, memory and learning, anxiety and depression (Heilig, 2004; Sajdyk, 2005; Tasan et al., 2009).

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 alter significantly the pharmacokinetics or the anti-coagulant activity of warfarin. It was concluded that SHR-5 might be of value in the treatment of patients with mild or moderate depression, and that its interaction with co-administered drugs is likely to be negligible (Panossian et al., 2008b).

Clinical trials in humans

Post-Russian 'Western' research on Rhodiola has grown over the past decade. Results of some clinical trials are discussed in several review articles (Kelly, 2001; Brown et al., 2002; Khanum et al., 2005; Walker and Robergs, 2006; Blomkvist et al., 2009; Panossian and Wikman, 2009a,b). In total, more than 30 publications on clinical efficacy of various Rhodiola preparations can be found in Pubmed database. The majority of these studies (of varying methodological rigor) are related to efficacy of Rhodiola on cognitive functions and mental performance in fatigue. Results of these studies are summarized in Tables 1–3.

Table 3
Results of randomized studies on humans involving effects of Rhodiola preparations on mental performance related to fatigue

Plant name	Study design[a]	Total subjects (sample size of verum/control) [age range]	Intervention/control dosage	Primary endpoint[b]	Main results[b]	Frequency of adverse effects	Quality level of evidence*	Jadad score (max 5) (Jadad et al., 1996)	Ref.
Rhodiola rosea	PC 2 parallel groups	60 volunteers with stress-induced fatigue (30/30) [20-55 years]	Extract SHR-5 (288 mg twice daily)/ placebo for 4 weeks	Symptoms of fatigue, attention, depression, QOL, salivary cortisol	Symptoms of fatigue, attention and salivary cortisol significantly improved compared with control	None	Ib	5	Olsson et al., (2009)
	PC, CO 2 parallel groups	56 healthy subjects (?/?)[c] [24-35 years]	Extract SHR-5 (170 mg once daily)/ placebo for 2 weeks	Mental fatigue, perceptive and cognitive functions such as associative thinking, short-term memory, calculation and ability of concentration, and speed of audio-visual perception	Statistically significant improvement in the treatment group (SHR-5) during the first 2 week period	None	Ib	4	Darbinyan et al., (2000)
	PC 2 parallel groups	40 healthy subjects (20/20) [17-19 years]	Extract SHR-5 (50 mg twice daily)/placebo for 20 days	Mental fatigue, physical performance, general well-being	Significant improvement in physical fitness, mental fatigue and neuromotor tests compared with control ($p < 0.01$). 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 neuromuscular tapping test	None	Ib	3	Spasov et al. 2000
	PC 3 parallel treatment groups	161 healthy subjects, (41/20/40 treated + 20 untreated) [19-21 years]	Extract SHR-5 (single dose of 370 mg or 555 mg) /placebo	Capacity for mental work	Significant difference in anti-fatigue effects in SHR-5 groups compared with control ($p < 0.001$), whilst no significant difference between the two dosage groups was observed	One subject in placebo group complained of hyper-salivation lasting 40 min after intake	Ib	3	Shevtsov et al., (2003)
	PC 3 parallel treatment groups	91 patients with mild and moderate depression (31/30/30) [18-70 years]	Extract SHR-5 (170 mg or 340 mg twice daily)/placebo for 6 weeks	Depression in total HAMD and BDI scores	Significant differences in HAMD and BDI scores and scores reflecting levels of insomnia, emotional instability, somatisation and self-esteem in SHR-5 groups compared to placebo ($p < 0.001$)	None	Ib	5	Darbinyan et al., (2007)

[a] CO - crossover; PC - placebo-controlled; M – multi-centre;
[b] QOL – quality of life; HAMD - Hamilton Depression Rating Scale; BDI - Beck Depression Inventory; RVI – Rand Vitality Index; HR – heart rate; BP – blood pressure; CDR – Cognitive Drug Research; MMSE – Mini-mental State Examination; ADAS – Alzheimer Disease Assessment Scale; CDRS – Clinical Dementia Rating Scale;
* According to WHO, FDA and EMEA: Ia - meta-analyses of randomized and controlled studies; Ib - evidence from at least one randomized study with control ; IIa - evidence from at least one well-performed study with control group; IIb - evidence from at least one well-performed quasi-experimental study; III - evidence from well-performed non-experimental descriptive studies as well as comparative studies, correlation studies and case-studies; and IV - evidence from expert committee reports or appraisals and/or clinical experiences by prominent authorities.

A systematic review of these studies shows that Rhodiola SHR-5 standardized extract demonstrate significant beneficial specific effects on stress-induced symptoms in fatigue (Panossian and Wikman, 2009). For instance in patients with fatigue syndrome, classified as a reaction to severe stress (subjects must exhibit daily symptoms of fatigue, enduring for at least 2 weeks, related to a specific stressor that has been present for at least 6 months, and their daily functioning must be significantly negatively affected). Rhodiola significantly reduced symptoms of fatigue and improved attention after four weeks of repeated administration (Olsson et al., 2009). Additionally, it was suggested that the inhibitory effect of Rhodiola on the increased basal level of salivary cortisol results in an improvement in cognitive function. This proposal is in line with other studies demonstrating that optimal corticosteroid levels are a requirement for efficient cognitive function since significant changes (up or down) in circulating levels of corticosteroids results in cognitive impairment (Herbert et al., 2006). The anti-fatigue effect of Rhodiola SHR-5 extract, together with improvement in cognitive functions in fatigue and under stressful conditions, have been reported in healthy volunteers who had received single and repeated doses of the medication (Darbinyan et al., 2000; Spasov et al., 2000; Shevtsov et al., 2003). It is concluded that repeated administration of *R. rosea* extract SHR-5 exerts an anti-fatigue effect that increases mental performance, particularly the ability to concentrate in healthy subjects and burnout patients with fatigue syndrome.

Results of five clinical trials examining ergogenic properties of *Rhodiola rosea* are conflicting. Statistically significant improvement of physical performance measured as PWC-170 in ergometry test, and as oxygen uptake peak in endurance exercise capacity tests (Spasov et al., 2000; De Bock et al., 2004) was found in two studies, while for the majority of other parameters, such as muscle strength, peak power, ventilatory threshold, lactate threshold and oxygen uptake, tested in tree studies, Rhodiola did not demonstrate significant difference compared to placebo groups (De Bock et al., 2004; Earnest et al., 2004; Colson et al., 2005).

One of the most important subjects of discussion is related to seemingly contradictory results of different studies where some Rhodiola preparations were effective, while some other not (De Bock et al., 2004; Earnest et al., 2004; Colson et al., 2005). Possible explanation of this might be found when two important circumstances are taken into account: dose-effect dependence pattern and variety in composition of active constituents of different preparation. The effect of Rhodiola on CNS, and other body systems does not depend linearly on the dose. The dose dependent curve has a bell shape: in small doses Rhodiola is inactive, in intermediate dose level active, and in high dosed inactive again (Kurkin et al., 2003; Perfumi and Mattioli, 2007; Wiegant et al. 2009 ; Schriner et al., 2009). This phenomenon is well known in pharmacology and can have different explanations, including feedback regulation of several signaling systems, working in parallel in a whole body/system level. These mechanisms are very specific for many systems and yet not fully scientifically investigated.

It can be suggested that in some studies where effect was not observed the dose of Rhodiola was inappropriate, e.g. De Bock et al., 2004; Earnest et al., 2004; Colson et al., 2005 studies, where only one dose was used. It must be pointed out that the content of active ingredients in herbal preparations depends on many factors, such as in which geographic and climate zone it was grown, in which season and whether conditions it was harvested, how it was dried, extracted and prepared into final dosage form. For example, a high degree of inter clone variation was found for all tested constituents (salidroside, tyrosol, rosavin, rosarin, rosin and cinnamic alcohol) in six samples of *Rhodiola rosea* roots collected in various regions of Norway. The highest variation was found for Salidroside and tyrosol, showing an inter clone variation of 92.8 and 87.8%, respectively (Hellum et al., 2009). Therefore, the preparations obtained by different producers can have quite different active dose level.

"A randomized double-blind placebo controlled parallelgroup study of SHR-5 extract of *Rhodiola rosea* roots as treatment for patients with stress related fatigue" by Olsson et al, published in *Planta medica.* 2009, 75:105-112, clearly demonstrated an antifatigue and attention improving effect of a *Rhodiola rosea* extract (SHR-5) in patients with stress-induced fatigue. The authors pointed out that these results were in line with other studies demonstrating an antifatigue effect together with an increase of mental work capacity (quantitatively/qualitatively) against a background of strain and stress, which is characteristic of an adaptogen. This conclusion is questioned in a recent review article "Perspective on Roseroot (*Rhodiola rosea*) studies" by Blomkvist et al., 2009 saying "(the mentioned study) appears to be the only one among these we have investigated has used a satisfactory experimental protocol and statistical methods".

While we respect some of the conclusions made by the authors, and support further more robust studies of Rhodiola, our review of the evidence (detailed in Tables 1–3) provides a different perspective to the Blomkvist et al. 2009 review. The quality assessment seems to be according to a binary scale, 0 or 1, (the authors are not explicitly stating this but is implied from their discussion). The attention of this paper is "focused mainly on the statistical analysis to determine if conclusions (of published articles) are valid". While they have pointed out many pertinent minor weaknesses, it is adventurous to challenge the efficacy of interventions primarily on findings of technical errors in a sample of selected articles.

It might be appropriate in this context to point out some misunderstandings due to printing errors. For instance in Darbinyan et al. (2007) study in Tables 2 and 3 a misprint "paired" – instead of "unpaired" t-test was published. Actually, unpaired t-test was used originally in that study and the difference between groups is very significant. However, if this method would have been used, a comparison in both groups would yield even higher significance.

Conclusions

Rhodiola rosea L. is a popular plant in traditional medical systems in the Nordic countries, Eastern Europe and Asia, with a reputation for stimulating the nervous system, decreasing depression, enhancing work performance, eliminating fatigue, and preventing high altitude sickness. The traditional medicinal use of the plant, in addition to modern clinical use as referenced in scientific publications and official pharmacopoeias contribute to substantiate the well-established medicinal use.

Based on the proposed mechanism of action and available experimental data, Rhodiola appears to offer an advantage over other adaptogens in circumstances of acute stress. A single dose of *Rhodiola rosea* (SHR-5) prior to acute stress produces favorable results and prevents stress-induced disruptions in function and performance. Since many stressful situations are acute in nature, and sometimes unexpected, an adaptogen that can be taken acutely in these circumstances, rather than requiring chronic advance supplementation, could be potentially very useful.

Rhodiola also offers some cardio-protective benefits not associated with other adaptogens. Its proposed ability to moderate stress-induced damage and dysfunction in cardiovascular tissue might make Rhodiola the adaptogen of choice among patients at higher risks for cardiovascular disease (Maslov et al., 1997). However, it is important to reproduce and confirm the non-clinical studies and plan for GCP conducted human trials.

The clearest emerging indication for *Rhodiola rosea* preparation is as a drug as a tonic during convalescence to increase both

mental and physical work capacity against a background of fatigue and/or stress.

Some animal and preliminary clinical evidence suggest the need for a well defined range of therapeutic dosage of Rhodiola.

It may be concluded from the review of evidence presented in this paper that encouraging support exists for Rhodiola's beneficial effect on cognitive function and fatigue, as demonstrated by numerous pre-clinical and several clinical studies. Rhodiola's adaptogenic effect increases attention and endurance in situations of decreased performance caused by fatigue and sensation of weakness, and reduces stress-induced impairments and disorders related to the function of neuro-endocrine and immune systems.

Conflicts of interest

J.Sarris declares no conflict of interest. G.Wikman and A.Panossian are associated with the Swedish Herbal Institute, a company that researches and commercialises Rhodiola -derived functional products.

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