REVIEW ARTICLE

Annals of Agricultural and Environmental Medicine 2015, Vol 22, No 2, 281–285
www.aaem.pl

Approaches of *Rhodiola kirilowii* and *Rhodiola rosea* field cultivation in Poland and their potential health benefits

Marta Grech-Baran[1], Katarzyna Sykłowska-Baranek[1], Agnieszka Pietrosiuk[1]

[1] *Department of Pharmaceutical Biology and Medicinal Plant Biotechnology, Faculty of Pharmacy, Poland*

Grech-Baran M, Sykłowska-Baranek K, Pietrosiuk A. Approaches of Rhodiola kirilowii and Rhodiola rosea field cultivation in Poland and their potential health benefits. Ann Agric Environ Med. 2015; 22(2): 281–285. doi: 10.5604/12321966.1152081

Abstract

Numerous researches have been carried out on plants of the *Rhodiola* species, especially *Rhodiola kirilowii* (Regel) Maxim. and *Rhodiola rosea*. Various compounds have been reported to be isolated from *R. kirilowii* and *R. rosea,* including cyanogenic glycosides, monoterpene alcohols and their glycosides, aryl glycosides, phenylethanoids, phenylpropanoids and their glycosides (salidroside and rosavins respectively), as well as flavonoids, flavonlignans, proanthocyanidins and gallic acid derivatives and the latter have free radical scavenging capacity. The benefits claimed for *Rhodiola* include adapogenic, neuroprotective, anti-depresive anti-tumour and cardioprotective activities. Currently, the adaptogenic activity of *Rhodiola* compounds are properties evaluated mainly in human clinical trials. The mechanism of the action of *Rhodiola* extracts include affecting the levels of cortisol and NO by interactions with glucocorticoid receptors directly or via the c-Jun N-terminal protein kinase (JNK) pathway. However, the natural populations of *R. rosea* in Poland are threatened; therefore, the cultivation of *R. rosea* and alternative species *R. kirilowii* might be a possible solution for producing these kinds of plants in Poland in sufficient quantities and quality for pharmaceutical purposes. Lack of proven interaction with other drugs and no confirmed adverse effects during clinical trials encourages further investigation. These herb preparations ought to be studied extensively to establish their position as potential drugs for a variety of diseases.

Key words

Rhodiola kirilowii, *Rhodiola rosea*, cultivation, salidroside, rosavins

INTRODUCTION

In pharmacy, plant raw materials are important sources of new medicines and their substitutes. Natural medicines of plant origin have a wider therapeutic spectrum, milder action and less frequent side-effects, compared with synthetic substances [1].

The rhizomes of *Rhodiola spp.* (*Crassulaceae*) can be found in the wild in many mountainous regions of the northern, central, and south-eastern parts of Europe, as well as in central and northern Asia, the sub-arctic and Siberia, and the mountains of Altai and Mongolia [2]. Their medicinal functionality have been broadly discussed and accepted in folk medicine. Traditionally, *Rhodiola* have been used to stimulate the nervous system through decreasing depression, enhancing work performance, eliminating fatigue, and preventing high altitude sickness [3]. Currently, mainly the adaptogenic properties of *Rhodiola* preparations are considered as potential drugs for clinical trials. Adaptogens are known as a pharmacotherapeutic group of herbal preparations used to increase attention endurance in fatigue, and prevent/mitigate/reduce stress-induced impairments and disorders related to the neuro-endocrine and immune systems [4].

Due to intensive harvesting, the natural populations of *R. rosea* and *R. kirilowii* are highly threatened and have been included in the list of endangered plant species in many countries [5], including Russia, the United Kingdom, Czech Republic, Bosnia and Herzegovina, Slovakia and Bulgaria, where its collection is strictly forbidden [6]. In Poland, *R. rosea* can be found in the national parks of the Tatra Mountain, on Babia Góra, and the Bieszczady Mountains, and is not red listed. Contrary to the well-investigated *R. rosea, R. kirilowii* is fairly new in Poland and has been cultivated in the Garden of Medicinal Plants in Plewiska near Poznan [7].

According to the natural ecological requirements, *Rhodiola* could be successfully cultivated in climatically cool and sufficiently moist areas, with equal distribution of precipitation [2]. Experimental field cultivation was established in Poland in 2000 [8], and during 2005–2011 studies were conducted in experimental fields at the University of Agriculture in Lublin. The obtained results showed that plants harvested for rhizomes may be obtained after five years of cultivation [5]. It was demonstrated that *Rhodiol*a could be effectively cropped both in ecological and conventional system by Polish farmers [9]. The cultivation of these plants on a wide spread scale, especially in southern Poland, would be profitable for obtaining valuable plant material. Lack of any proven interaction with other drugs and no confirmed adverse effects in the course of clinical trials make it potentially attractive as a source for producing medications by pharmaceuticals companies.

Chemical composition. The published literature specifies more than 135 different species of *Rhodiola* identified during taxonomic study, of which at least 20 are in the evaluating process in medical trials. Various compounds have been reported to be isolated from *Rhodiola* [4, 10, 11, 7] which are suspected of having potential for being a reliable drug

Address for correspondence: Katarzyna Syklowska-Baranek, Department of Pharmaceutical Biology and Medicinal Plant Biotechnology, Faculty of Pharmacy, Poland, Banacha 1, 02-097 Warsaw, Poland
E-mail: ksyklowska@yahoo.com

Received: 04 April 2013; accepted: 06 February 2014

candidate for various diseases. The herein review presented and highlighted two species which are credited for their pharmacological activity: *Rhodiola rosea* and *Rhodiola kirilowii*.

The roots and rhizomes of *Rhodiola* have been reported to contain distinct groups of chemical compounds: phenylethanol derivatives: salidroside (rhodioloside) tyrosol monoterpenes: rosiridol, rosaridin, triterpenes: daucosterol, beta-sitosterol, flavanoids: rodiolin, rodionin, rodiosin, acetylrodalgin, tricin epigallocatechin, epicatechin and phenolic acids: chlorogenic, hydroxycinnamic and gallic acids [10, 12].

Nevertheless, there is a diversification related to each species: *R. rosea* and *R. kirilowii* contain cynnamyl alcohol and its glycosides – phenylpropanoids: rosavin, rosin, rosarin (rosavins being the general term for all three). These compounds are a characteristic feature of *Rhodiola rosea* which were not detected in the other 21 morphologically-similar *Rhodiola* species [4, 13]. They are also responsible for adaptogenic properties of both *R. rosea* and *R. kirilowii*. Further investigations of *R. rosea* indicated that the dried rhizomes contained 0.05% essential oil [11]. The studies on the phytochemistry of *R. kirilowii* revealed that the hydrophilic extract contains coumarins, esculetin, umbelliferone, flavonoid herbacitrin and bergenin [14]. Moreover, the latest research indicates that *R. kirilowii* includes rhodiocyanoside A, lotaustralin-cyanogenic glycoside [15]. So far, the most investigated in clinical trials of all the presented constituents are salidroside and rosavins.

Multipotential bioactivities of *Rhodiola* extract and phenolic glycosides. In the light of many civilization diseases [16, 17, 18], *Rhodiola* has been investigated for its potential effectiveness in *in vitro* as well as in *in vivo* various biological studies. Table 1 summarized all the experimental findings related to *R. rosea* and *R. kirilowii* and their therapeutic usage.

Immunity increasing and immune-modulatory effect. The *in vivo* and *in vitro* immunomodulation activity of 50% hydro-alcoholic extract of *R. kirilowii* on cellular immunity parameters in mice and rats was investigated [19]. The obtained results revealed that both extracts stimulated *in vitro* granulocyte activity and increased lymphocyte response to mitogens. *In vivo* the extracts enhanced the ability of lymphocytes to induce local cutaneous graft-versus-host reaction (GVH). Further research showed potential *in vitro* modulatory function of aqueous and hydro-alcoholic extracts of under-ground parts of *R. kirilowii* on respiratory burst activity (RBA), and on the proliferative response to lipopolysaccharide (LPS) in blood leukocyte cultures of pigs. The results indicated that both extracts in concentrations up to 10 μg/ml stimulated this parameter [20]. The diminishing influence of *Rhodiola* extracts on *Pseudomonas aeruginosa* infection in mice was also demonstrated. Feeding mice with extracts significantly increased blood lymphocytes and granulocytes number.

Anti-viral activity. The inhibitory activity of ethanol extract of *R. kirlowii* against HCV-NS3-SP serine protease was measured. Epicatechin derivatives isolated from the

Table 1. Summary of experimental findings on medicinal properties of *Rhodiola rosea* and *Rhodiola kirilowii*

Species	Kind of extract	Type of study	Bioactivity	References
Rhodiola kirilowii	Ethanol extract	*In vitro*	Anti- viral	[21]
Rhodiola rosea	Salidroside	*In vitro* and *in vivo*	Anti- viral	[22]
Rhodiola kirilowii	Water and 50% hydro-alcoholic extract	*In vitro*	Immune-modulatory	[19]
Rhodiola kirilowii	Water and 50% hydro-alcoholic extract	*In vitro* and *in vivo*	Immunity increasing	[20]
Rhodiola rosea	Ethanol- extract 50mg/kg	*In vivo*	Anti-fatigue	[40]
Rhodiola rosea	Salidroside	*In vivo*	Anti-fatigue	[41]
Rhodiola rosea	RHODAX (340 mg of siccum extract)	*In vivo*	Anti-depressive	[42]
Rhodiola rosea	Ethanol extract	*In vivo*	Anti-depressive	[23]
Rhodiola rosea	Methanol extract, water extracts	*In vitro*	Anti-depressive	[24]
Rhodiola rosea	Extract	*In vitro*	Antioxidant	[43]
Rhodiola rosea	Salidroside	*In vitro*	Antioxidant	[27]
Rhodiola rosea	Water extract	*In vitro*	Antioxidant	[28]
Rhodiola rosea	Salidroside	*In vitro*	Cardioprotective	[25]
Rhodiola rosea	Ethanol extract	*In vivo*	Increasing myocardial performance	[26]
Rhodiola rosea	Salidroside	*In vitro*	Anti-hypoxia	[29]
Rhodiola rosea	Water and 50% hydro-alcoholic extracts rosavin	*In vitro* and *in vivo*	Angiogenesis inhibition	[44]
Rhodiola rosea	Salidroside	*In vitro*	Anti-metastasis effect	[30]
Rhodiola rosea	Homogenous polysaccharide (RRP-*ws*)	*In vitro and in vivo*	Anti-tumour, and immunity increasing	[31]
Rhodiola kirilowii	Water and 50% hydro-alcoholic extract rosavin	*In vitro and in vivo*	Anti-tumour activity	[32]
Rhodiola rosea	Salidroside	*In vitro*	Neuroprotective	[33]
Rhodiola rosea	Salidroside	*In vitro*	Neuroprotective	[45]
Rhodiola rosea	Ethanol extract separated into chloroform, ethyl acetate, n-butanol, water fractions	*In vitro*	Anti-Acetylcholinoesterase Inhibitory	[46]
Rhodiola rosea	Salidroside	*In vitro*	Neuroprotective	[34]
Rhodiola rosea	Salidrosie, tyrosol galactoside	*In vitro and in vivo*	Neuroprotective against focal cerebral ischemia	[35]

extract demonstrated strong anti-viral potential [21]. As non-peptide inhibitors of HCV-NS3-SP these compounds may serve as a potential candidate for anti-HCV agents. Moreover, salidroside *in vitro* on rats myocardial cells or *in vivo* on mice exhibited an anti-viral effect against coxsackievirus B3. Reverse transcription polymerase chain reaction (Rt-PCR) of heart cells showed that salidroside modulated mRNA expression on INF-γ, interleukin 10 and TNFα [22].

Anti-depressive activity. *In vivo R. rosea* could improve the 5-HT level in rat hippocampus after oral administration. At low dosages (1.5 g/kg), ethanolic extract induced stem cell proliferation and repair of injured hippocampus neurons, returning them to normal level [23]. It was also demonstrated that the methanol and water extracts of *R. rosea* respectively exhibited inhibitions of 92.5% and 84.3% MAO A and 81.8% and 88.9% on MAO B at a concentration of 100 μg/ml [24].

Increasing miocardial performance. The cardio-protection activity of salidroside from ischemia and reperfusion was investigated [25]. The results suggested that salidroside significantly increased *O*-linked N- acetyl- glucosamine level associated with decreased cardiomyocytes injury. In further studies, the influence of *Rhodiola* ethanol extract *in vivo* in STZ-diabetic rats was determined. The extract increased the level of PRARδ (Ligand activate transcriptional factor), and regulated gens expression involved in the maintenance of inotropic function in cardiomyocytes [26]. It also caused a rise in cardiac output without any changes in the diabetic parameters.

Anti-oxidant and anti-anoxia activities. Salidroside (5μM) was able to prevent morphological changes in cultured human foetal lung fibroblast (2BS cells model) after a sub-lethal dose of H_2O_2. The implicated treatment abrogated G1 arrest and promoted cells re-entry into S and G2/M phase [27]. In *in vitro* test on human keratinocyte line, the applied *R. rosea* extract, in a time dose dependent-manner, increased activity of trans-plasma membrane oxido reductase activity. Moreover, the data obtained from that extract improved the activities of SOD (Superoxide dismutase) and CAT (Catalase) enzyme [28]. Further research revealed that salidroside might also act as a factor preventing hypoxia. Hypoxia is mainly mediated by hypoxia-inducible factor 1 (HIF-1). Saliroside pre-treatment notably decreased the level of HIF-1α and BACE-1 (β-Site amyloid precursor protein cleaving enzyme) in SH-SY5Y cells [29].

Anti-tumour activity. Recent research on *Rhodiola* has demonstrated that extracts containing salidroside and rosavins are potential drugs for the treatment of a number of cancers – the effect of salidroside on human fibrolastoma cells *in vitro* was determined. The results indicated that salidroside treatment increased tissue inhibitor on metalloproteinase -2 in a dose-dependent manner. It also demonstrated the inhibition of the activation of protein kinase, and phosphorylation of extracellular signal-regulated kinase 1 and 2 [30]. In recent years, numerous polysaccharides have been isolated from plants and used as a promising source of therapeutic agents for cancer. The lipopolysaccharide from *R. rosea* (RRP-*ws*) was tested using sarcoma cells both in *in vitro* and *in vivo* (in mice) studies. *In vitro* tests revealed direct cytotoxic effect on the growth of sarcoma cells. In *in vivo,* the growth of transplanted tumours was inhibited. Furthermore, RRP-*ws* increased the production of IL-2, TNF-α, INF-γ in serum and the ratio of CD4+/CD8+ T-lymphocyte on peripheral blood in tumour-bearing mice [31].

In the last investigation of *R. kirilowii* the effect of an aqueous and hydroalcoholic extract *in vivo* on cutaneous angiogenesis induced in mice by grafting sarcoma L- cells were observed. In *in vitro* studies, the influence of the extracts on the migration and proliferation of murine endothelial (HECa10) cells and on the proliferation of murine tumour (L-1 sarcoma) cells in tissue culture was measured. The results showed that in mice only hydroalcoholic extract administrated orally successfully suppressed neovascular reaction to L-1 sarcoma cells. *In vitro*, experiments showed that both extracts stimulated the proliferation of HECa10 cells, and both of them suppressed proliferation of L-1 sarcoma cells [32].

Neuroprotective activity. The neuroprotective efficiency of salidroside was investigated. The obtained results confirmed that salidroside at a concentration of 1–10 μmol/L could protect PC12cells (used as model neuron cells) against injures caused by exposure of 2 mm/L glutamate for 15 min [33]. In further research, the authors reported the protective salidroside activity on H_2O_2-induced cell apoptosis in nerve growth factor (NGF) differentiated PC12-cells. The results suggested that the neuroprotective effect of salidroside might be modulated by extracellular signal-regulated kinase (ERK) signaling pathway at the level of caspase-3 activation [34]. Recent studies indicate neuroprotective effect of salidroside (Sal) and tyrosol galactoside (Tyr) against cerebral ischema and neurotoxity. *In vivo,* Sal and Tyr significantly attenuated the effect of apoptosis and necrosis induced by oxidative insult in rat cortical neurons. Western blot analysis revealed that Sal and Tyr decreased the expression of Bax (Bcl-2-associated X protein) and restored the balance of pro and anty-apoptic protein. In comparison to Sal, Tyr has a better oxidative action [35].

Adaptogenic activity. Various mechanism of action of adapotogenic activities of *Rhodiola* related to its clinical effect have been proposed. Results of both human [36] and animal studies [37] revealed that the key point of action could be conducted with an up-regulating effect on stress-sensor protein Hsp70 which inhibits the expression of NO synthase II gene, and interacts with glucocorticoid receptors directly and *via* the JNK (c-Jun NH_2-terminal kinase) pathway, thus affecting the levels of circulating cortisol and NO [38]. Prevention of stress-induced increase in NO, and the associated decrease in ATP production, results in increased performance and endurance. Adaptogens also 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 [39]. Studies on the clinical effect of *Rhodiola* preparation are focused mainly on its efficiency on mental performance in fatigue, and on its influence on cognitive function. Results of randomized studies on humans involving the effects of *Rhodiola* are described in Table 2.

Table 2. Results of randomized studies on humans involving *R. rosea*

Species	Investigated group	Dose	Indication for use	Effects recorded	References
Rhodiola rosea	double-blind, cross-over study	SHR-5 extract (170 mg once daily)	Symptoms of fatigue and stress	Statistically significant improvement after 2 weeks of taking SHR-5 ($p < 0.01$) in treatment groups	[47]
Rhodiola rosea	double-blind, randomized placebo-controlled study	*Rhodiola rosea* extractum siccum radix -SHR- 5(50 mg twice daily)	Symptoms of fatigue	Notable improvement in psychomotoric function and mental fatigue, compared with control ($p< 0.01$)	[48]
Rhodiola rosea	Double-blind, randomized placebo-controlled study	SHR-5 extract (single dose 370 or 555 mg)	Symptoms of fatigue	Significant difference in anti-fatigue effect in SHR-5 groups, compared with control ($p < 0.001$)	[49]
Rhodiola rosea	double-blind randomised, placebo-controlled, parallel-group study	SHR- 5 extract (288 mg twice daily)	Symptoms of fatigue	Improvement in attention and mental fatigue	[36]
Rhodiola rosea	Double-blind, randomized placebo-controlled study	Single dose of 270 mg of ADAPT-232 (standardized fixed combination of *R. rosea, Schisandra chinensis* and *Eleutherococcus senticosus* extracts)	Increased mental performance, e.g. attention, speed and accuracy	Significant difference ($p<0.05$) in attention, speed, and accuracy between treatment and control group.	[50]

CONCLUSIONS

Rhodiola exhibited certain opportunities as a potential drug for use in health care, that indicating the need to spread the cultivation of *R. rosea* and *R. kirilowii* in Poland where advantageous environmental conditions exist. Encouraging results from human clinical trials with the usage of *R. rosea* extract contribute to being considered notable for its adaptogenic potential. Moreover, the results of a number of preclinical investigations have revealed that bioactive compounds from these plants are effective against many types of cancer. These extracts also demonstrated strong antioxidant and neuroprotective abilities. In spite of serious neurodegenerative diseases, *Rhodiola* preparations in the future could significantly increase the quality of life-span.

REFERENCES

1. Raila A, Lugauskas A, Kemzūraitė A, Zvicevičius E, Ragažinskienė O, Railienė M. Different drying technologies and alternation of mycobiots in the raw material of *Hyssopus officinalis* L. Ann Agric Environ Med. 2009; 16(1): 93–101.
2. Galambosi B. Demand and Availability of Rhodiola rosea L. Raw Material. Bogers R. Craker L, Lange D (eds.). Med Arom Plants Springer. 2006; 223–236.
3. Kelly GS. *Rhodiola rosea*: a possible plant adaptogen. Alter Medicine Rev. 2001; 6(3): 293–302.
4. Panossian A, Wikman G, Sarris J. Rosenroot (*Rhodiola rosea*): traditional use, chemical composition, pharmacology and clinical efficacy. Phytomed. 2010; 17(7): 481–493.
5. Kołodziej B, Sugier D. Selected elements of biology and morphology of Roseroot in south – eastern Poland. Acta Sci. Pol Hortorum Cultus. 2012; 11(5): 127–142.
6. Platikanov S, Evstatieva L. Introduction of wild golden root (*Rhodiala rosea* L.) as a potential economic crop in Bulgaria. Economic Botany 2008; 64(4): 621–627.
7. Krajewska-Patan A, Furmanowa M, Dreger M, Mścisz A, Mielcarek S, Kania M et al. *Rhodiola kirilowii* – the present status and perspectives of medicinal use Part I. *In vivo* and *in vitro* cultivation as well as phytochemical investigations of extracts of roots and callus tissues. Herba Pol. 2008; 54(4): 140–157.
8. Buchwald W, Mścirz A, Krajewska-Patan A, Furmanowa M, Mielcarek S. Mrozinkiewicz PM. Contents of biologically active compounds in *Rhodiola rosea* during vegetation period. Herba Pol. 2006; 52(4): 34–43.
9. Kucharski W, Mordalski R, Buchwald W, Mielcarek S. Roseroot – the comparison of tillage in conventional and ecological system. J Res Appl Agric Eng. 2011; 56(3): 232–235.
10. Saratikov AS, Krasnov EA, Khnikina LA, Duvidson LM. Isolation and chemical analysis of individual biologically active constituents of *Rhodiola rosea*. Proc Siberian Acad Sc Biol. 1967; 1: 54–60.
11. Rohloff J. Volatiles from rhizomes of *Rhodiola rosea* L. Phytochem. 2002; 59(6): 655–661.
12. Kurkin VA, Zapesochnaya GG. Chemical composition and pharmacological characteristics of *Rhodiola rosea*. J Med Plants. 1985; 1231–1445.
13. Yousef GG, Grace MH, Cheng DM, Belolipov IV, Raskin I, Lila MA. Comparative phytochemical characterization of three *Rhodiola* species. Phytochem. 2006; 67(21): 2380–2391.
14. Krasnov EA, Kuvaiev VB, Chorużaya TG. Chemotaksonomic investigations of *Rhodiola* sp. Rast Res. 1978; 14(2): 153–160.
15. Wiedenfeld H, Zych M, Buchwald W, Furmanowa M. New compounds from *Rhodiola kirilowii*. Scientia Pharm. 2007; 34: 29–34.
16. Wojtyła A. Differences in health – a global problem and its various aspects. Ann Agric Environ Med. 2011; 18(2): 191–192.
17. Krzyzak M, Maslach D, Juczewska M, Lasota W, Rabczenko D, Marcinkowski J, Szpak A. Differences in breast cancer incidence and stage distribution between urban and rural female population in Podlaskie Voivodship, Poland in years 2001–2002. Ann Agric Environ Med. 2010; 17(1): 159–162.
18. Bojar I, Cvejić R, Głowacka MD, Koprowicz A, Humeniuk E, Owoc A. Morbidity and mortality due to cervical cancer in Poland after introduction of the Act – National Programme for Control of Cancerous Diseases. Ann Agric Environ Med. 2012; 19(4): 680–685.
19. Wójcik R, Siwicki AK, Skopińska-Różewska E, Wasiutyński A, Sommer E, Furmanowa M. The effect of Chinese medicinal herb *Rhodiola kirilowii* extracts on cellular immunity in mice and rats. Pol J Vet Sci. 2009; 12(3): 399–405.
20. Siwicki AK, Skopińska-Różewska E, Wasiutyński A, Wójcik R, Zdanowski R, Sommer E. The effect of *Rhodiola kirilowii* extracts on pigs' blood leukocytes metabolic (RBA) and proliferative (LPS) activity, and on the bacterial infection and blood leukocytes number in mice. Centr Eur J Immunol. 2012; 37(2): 145–150.
21. Zuo G, Li Z, Chen L, Xu X. Activity of compounds from Chinese herbal medicine *Rhodiola kirilowii* (Regel) Maxim against HCV NS3 serine protease. Antiviral Res. 2007; 76(1): 86–92.
22. Wang H, Ding Y, Zhou J, Sun X, Wang S. The in vitro and in vivo antiviral effects of salidroside from *Rhodiola rosea* L. against coxsackievirus B3. Phytomed. 2009;16(2–3): 146–155.
23. Chen QG, Zeng YS, Qu ZQ, Tang JY. Qin YJ, Chung P, et al. The effects of *Rhodiola rosea* extract on 5-HT level, cell proliferation and quantity of neurons at cerebral hippocampus of depressive rats. Phytomed. 2009; 16(9): 830–838.
24. Van Diermen D, Marston A, Bravo J, Reist M, Carrupt PA, Hostettmann K. Monoamine oxidase inhibition by *Rhodiola rosea* L. roots. J Ethnopharmacol. 2009; 22(2): 397–401.
25. Wu T, Zhou H, Jin Z, Bi S, Yang X, Yi D, et al. Cardioprotection of salidroside from ischemia/reperfusion injury by increasing N-acetylglucosamine linkage to cellular proteins. Eur Jo Pharmacol. 2009; 613(1–3): 93–99.
26. Cheng YZ, Chen LJ. Lee WJ, Chen MF, Jung Lin H, Cheng JT. Increase of myocardial performance by *Rhodiola*-ethanol extract in diabetic rats. J Ethnopharmacol. 2012; 2: 234–239.
27. Mao G, Wang Y, Qiu Q, Yuan L, Li R, et al. Salidroside protects human fibroblast cells from premature senescence induced by H_2O_2 partly through modulating oxidative status. Mech Ageing Dev. 2010; (11–12): 723–731.

28. Calcabrini C, De Bellis R, Mancini U, Cucchiarini L, Potenza L, De Sanctis R, et al. *Rhodiola rosea* ability to enrich cellular antioxidant defences of cultured human keratinocytes. Arch Dermatol Res. 2010; 302 (3): 191–200.
29. Li QY, Wang HM, Wang ZQ, Ma JF, Ding JQ, Chen SD. Salidroside attenuates hypoxia-induced abnormal processing of amyloid precursor protein by decreasing BACE1 expression in SH-SY5Y cells. Neurosc lett. 2010; 481(3): 154–158.
30. Sun C, Wang Z, Zheng Q, Zhang H. Salidroside inhibits migration and invasion of human fibrosarcoma HT1080 cells. Phytomed. 2012; 19(3–4): 355–363.
31. Cai Z, Li W, Wang H, Yan W, Zhou Y, Wang G, et al. Antitumor effects of a purified polysaccharide from *Rhodiola rosea* and its action mechanism. Carbohyd Polymers 2012; 90(1): 1296–300.
32. Zdanowski R, Skopińska-Rózewska E, Wasiutyński A, Skopiński P, Siwicki, AK, Sobiczewska E, et al. The effect of *Rhodiola kirilowii* extracts on tumor-induced angiogenesis in mice. Centr Eur J Immunol. 2012; 37(2): 131–139.
33. Cao LL, Guan-Hua D, Min-Wei W. The effect of salidroside on cell damage induced by glutamate and intracellular free calcium in PC12 cells. J Asian Nat Prod Res. 2006; 8(1–2): 159–165.
34. Yu S, Shen Y, Liu J, Ding F. Involvement of ERK1/2 pathway in neuroprotection by salidroside against hydrogen peroxide-induced apoptotic cell death. J Mol Neurosci. 2010; 40(3): 321–331.
35. Shi TS, Feng J, Xing Y, Wu X, Li N, Zhang Z, et al. Neuroprotective effects of Salidroside and its analogue tyrosol galactoside against focal cerebral ischemia *in vivo* and H_2O_2-induced neurotoxicity in vitro. Neurotoxicity Res. 2012; 21(4): 358–367.
36. Olsson EM, Schéele B, Panossian A. A randomised, double-blind, placebo-controlled, parallel-group study of the standardised extract shr-5 of the roots of *Rhodiola rosea* in the treatment of subjects with stress-related fatigue. Planta Med. 2009; 75(2): 2105–2112.
37. Panossian A, Nikoyan N, Ohanyan N, Hovhannisyan A, Abrahamyan H, Gabrielyan E, et al. Comparative study of *Rhodiola* preparations on behavioral despair of rats. Phytomed. 2008; 15(1–2): 84–91.
38. Panossian A, Wikman G. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. Curr Clin Pharmacol. 2009; 4(3): 198–219.
39. Wiegant FA, Surinova S, Ytsma E, Langelaar-Makkinje M, Wikman G, Post JA. Plant adaptogens increase lifespan and stress resistance in *C. elegans*. Biogerontology. 2009; 10(1): 27–42.
40. Abidov M, Grachev S, Seifulla RD, Ziegenfuss TN. Extract of *Rhodiola rosea* radix reduces the level of C-reactive protein and creatinine kinase in the blood. Bull Exp Biol Med. 2004; 138(1): 63–64.
41. Li M, Donglian C, Huaixing L, Bende T, Lihua S, Ying W. Anti-fatigue effects of salidroside in mice J Medical Coll PLA. 2008; 23(2): 88–93.
42. Bystritsky A, Kerwin L, Feusner JD. A pilot study of *Rhodiola rosea* (Rhodax) for generalized anxiety disorder (GAD). J Alter Complem Med. 2008; 14(2): 175–180.
43. Chen CH, Chan HC, Chu YT,. Ho HY, Chen PY, Lee TH, et al. Antioxidant activity of some plant extracts towards xanthine oxidase, lipoxygenase and tyrosinase. Molecules 2009; 8: 2947–2958.
44. Skopińska-Rózewska E, Malinowski M, Wasiutyński A, Sommer E, Furmanowa M, Mazurkiewicz M et al. The influence of *Rhodiola quadrifida* 50% hydro-alcoholic extract and salidroside on tumor-induced angiogenesis in mice. Pol J Vet Sci. 2008; 11(2): 97–104.
45. Zhang L, Yu H, Sun Y, Lin X, Chen B, Tan C, et al. Protective effects of salidroside on hydrogen peroxide-induced apoptosis in SH-SY5Y human neuroblastoma cells. Eur J Pharmacol. 2007; 564(1–3): 18–25.
46. Wang H, Zhou G, Gao X, Wang Y, Yao W. Acetylcholinesterase inhibitory-active components of *Rhodiola rosea* L. Food Chem. 2007; 105(1): 24–27.
47. Darbinyan V, Kteyan A, Panossian A, Gabrielian E, Wikman G, Wagner H. *Rhodiola rosea* in stress induced fatigue-a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. Phytomed. 2000; 7(5): 365–371.
48. Spasov AA, Wikman GK, Mandrikov VB, Mironova IANeumoin VV. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of *Rhodiola rosea* SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. Phytomed. 2000; 7(2): 85–89.
49. Shevtsov VA, Zholus BI, Shervarly VI, Vol VB, Korovin YP. A randomized trial of two different doses of a SHR-5 *Rhodiola rosea* extract versus placebo and control. Phytomed. 2003; 10(2–3): 95–105.
50. Aslanyan G, Amroyan E, Gabrielyan E, Nylander M, Wikman G, Panossian A. Double-blind, placebo-controlled, randomised study of single dose effects of ADAPT-232 on cognitive functions. Phytomed. 2010; 17(7): 494–499.