

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

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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, flavonolignans, proanthocyanidins and gallic acid derivatives and the latter have free radical scavenging capacity. The benefits claimed for *Rhodiola* include adaptogenic, neuroprotective, anti-depressive 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 *Rhodiola* 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

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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 (rhodiololide) tyrosol monoterpenes: rosiridol, rosaridin, triterpenes: daucosterol, beta-sitosterol, flavanoids: rodilin, rodionin, rodiosin, acetylrodalgin, triclin 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 cinnamyl 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 herbacetin 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. kirilowii* 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
<i>Rhodiola kirilowii</i>	Ethanol extract	<i>In vitro</i>	Anti-viral	[21]
<i>Rhodiola rosea</i>	Salidroside	<i>In vitro</i> and <i>in vivo</i>	Anti-viral	[22]
<i>Rhodiola kirilowii</i>	Water and 50% hydro-alcoholic extract	<i>In vitro</i>	Immune-modulatory	[19]
<i>Rhodiola kirilowii</i>	Water and 50% hydro-alcoholic extract	<i>In vitro</i> and <i>in vivo</i>	Immunity increasing	[20]
<i>Rhodiola rosea</i>	Ethanol- extract 50mg/kg	<i>In vivo</i>	Anti-fatigue	[40]
<i>Rhodiola rosea</i>	Salidroside	<i>In vivo</i>	Anti-fatigue	[41]
<i>Rhodiola rosea</i>	RHODAX (340 mg of siccum extract)	<i>In vivo</i>	Anti-depressive	[42]
<i>Rhodiola rosea</i>	Ethanol extract	<i>In vivo</i>	Anti-depressive	[23]
<i>Rhodiola rosea</i>	Methanol extract, water extracts	<i>In vitro</i>	Anti-depressive	[24]
<i>Rhodiola rosea</i>	Extract	<i>In vitro</i>	Antioxidant	[43]
<i>Rhodiola rosea</i>	Salidroside	<i>In vitro</i>	Antioxidant	[27]
<i>Rhodiola rosea</i>	Water extract	<i>In vitro</i>	Antioxidant	[28]
<i>Rhodiola rosea</i>	Salidroside	<i>In vitro</i>	Cardioprotective	[25]
<i>Rhodiola rosea</i>	Ethanol extract	<i>In vivo</i>	Increasing myocardial performance	[26]
<i>Rhodiola rosea</i>	Salidroside	<i>In vitro</i>	Anti-hypoxia	[29]
<i>Rhodiola rosea</i>	Water and 50% hydro-alcoholic extracts rosavin	<i>In vitro</i> and <i>in vivo</i>	Angiogenesis inhibition	[44]
<i>Rhodiola rosea</i>	Salidroside	<i>In vitro</i>	Anti-metastasis effect	[30]
<i>Rhodiola rosea</i>	Homogenous polysaccharide (RRP-ws)	<i>In vitro</i> and <i>in vivo</i>	Anti-tumour, and immunity increasing	[31]
<i>Rhodiola kirilowii</i>	Water and 50% hydro-alcoholic extract rosavin	<i>In vitro</i> and <i>in vivo</i>	Anti-tumour activity	[32]
<i>Rhodiola rosea</i>	Salidroside	<i>In vitro</i>	Neuroprotective	[33]
<i>Rhodiola rosea</i>	Salidroside	<i>In vitro</i>	Neuroprotective	[45]
<i>Rhodiola rosea</i>	Ethanol extract separated into chloroform, ethyl acetate, n-butanol, water fractions	<i>In vitro</i>	Anti-Acetylcholinesterase Inhibitory	[46]
<i>Rhodiola rosea</i>	Salidroside	<i>In vitro</i>	Neuroprotective	[34]
<i>Rhodiola rosea</i>	Salidroside, tyrosol galactoside	<i>In vitro</i> and <i>in vivo</i>	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 TNF α [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 μ g/ml [24].

Increasing myocardial 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 PRAR δ (Ligand activate transcriptional factor), and regulated genes 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 (5 μ M) was able to prevent morphological changes in cultured human foetal lung fibroblast (2BS cells model) after a sub-lethal dose of H₂O₂. 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-1 α 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 fibroblastoma 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 μ mol/L could protect PC12 cells (used as model neuron cells) against injuries caused by exposure of 2 mm/L glutamate for 15 min [33]. In further research, the authors reported the protective salidroside activity on H₂O₂-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 ischemia and neurotoxicity. *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 anti-apoptotic protein. In comparison to Sal, Tyr has a better oxidative action [35].

Adaptogenic activity. Various mechanism of action of adaptogenic 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 NH₂-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
<i>Rhodiola rosea</i>	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]
<i>Rhodiola rosea</i>	double-blind, randomized placebo-controlled study	<i>Rhodiola rosea</i> 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]
<i>Rhodiola rosea</i>	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]
<i>Rhodiola rosea</i>	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]
<i>Rhodiola rosea</i>	Double-blind, randomized placebo-controlled study	Single dose of 270 mg of ADAPT-232 (standardized fixed combination of <i>R. rosea</i> , <i>Schisandra chinensis</i> and <i>Eleutherococcus senticosus</i> 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.

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