RHODIOLA

Rhodiola rosea L.

Family

Crassulaceae.

Parts Used

Root.

Description

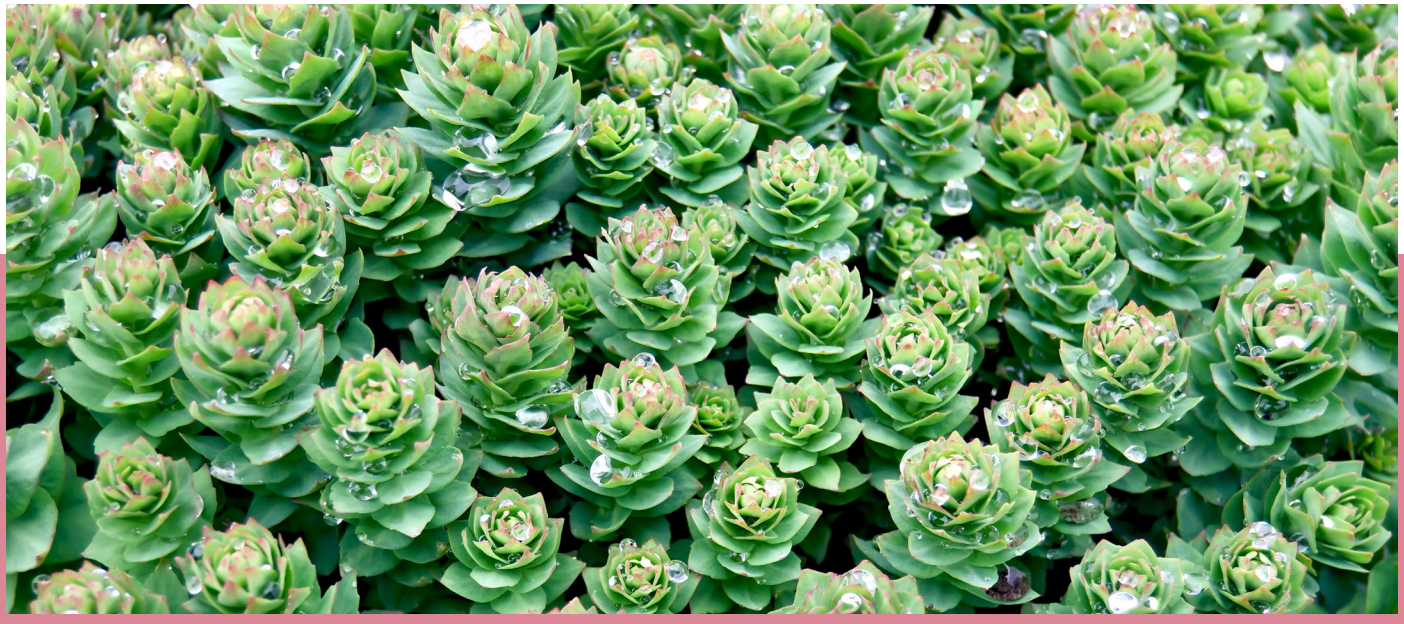
Rhodiola is native to cold northern alpine regions, and has been found in many harsh arctic and sub-arctic parts of the world including Central Asia, Scandinavia, Europe and the United States. A member of the Crassulaceae family, this hardy plant thrives on rocks, grassy and rocky slopes and crevices. Rhodiola is a perennial herb with a robust root system, which yields the mildly fragrant roots and rhizomes used in medicine. The erect stems range from 10 to 60cm high and the leaves are oblong. Rhodiola has yellow/pinkish unisexual flowers that appear throughout spring & summer.

Traditional Use

Rhodiola has been used as a medicinal herb for centuries throughout Northern Europe and Scandinavia. Its common name Roseroot or Golden Root refers to the golden coloured roots used in medicine. Rhodiola was well regarded traditionally for building strength, stamina and vitality in the harsh climates where it thrives. It was commonly employed for anaemia, fatigue and depression, as well as for infections, infertility, impotence and gastrointestinal ailments.

Constituents

The prominent constituents in rhodiola include phenylpropanoids (rosarin, rosavin, rosin -



collectively called rosavins in many studies), phenylethanol derivatives (salidroside, rhodioloside, tyrosol), flavanoids (rodiolin, rodionin, rodiosin, acetylrodalgin, tricin), monoterpernes (rosiridol, rosaridin), triterpenes (daucosterol, beta-sitosterol) and phenolic acids (chlorogenic and hydroxycinnamic, gallic acids).[1]

Actions

Adaptogen, antioxidant, antidepressant, anxiolytic, central nervous system stimulant, cardioprotective, anticancer, anti-inflammatory, hormonal regulator.

Pharmacological Activity

Adaptogen Activity

Rhodiola has been shown to possess adaptogenic activity in many studies. Numerous animal studies have found the herb to modulate the stress response – with recent studies suggesting that the molecular chaperones, heat shock proteins, are responsible for some of the effects.

A combination of siberian ginseng, schisandra and rhodiola strongly augmented endurance of mice, increasing the time taken to exhaustion approximately seven fold. The adaptogens increased levels of serum heat shock proteins (regarded as a defense response to stress), and this was postulated for the increased tolerance to physical and emotional stresses that the herbs offered.[2]

Another study found that adaptogens work through reprogramming transcriptional activities in cells favoring the synthesis of proteins involved in stress resistance (such as heat shock proteins) and longevity. Based on these observations, the authors suggested that adaptogens are experienced as mild stressors and thereby induce increased stress resistance and a longer lifespan.[3]

A further study found rhodiola to possess cardioprotective and antiarrhythmic effects that do not involve the heat shock proteins but through some other mechanism within the sympathetic nervous system.[4]

A study in rats examined whether rhodiola could counteract the poor feeding that is often induced by physical and psychological stress. Different doses of the herbs were used alongside different stress responses and also compared with anorexia induced by the drug fluoxetine (FLU) or by E.coli lipopolysaccharide (LPS). The herb was found to reverse the anorectic effects induced both by immobilisation of rats and by cortisol injection. The herb failed to reduce the anorectic effect induced both by LPS and FLU, and did not modify food intake in both freely-feeding and food-deprived rats. The findings strongly demonstrated that rhodiola is able to selectively attenuate stress-induced anorexia, providing functional evidence of claimed adaptogen and antistress properties.[5]

Another study examined the effects of rhodiola on binge eating in rats, as stress is a key determinant of binge eating (BE). Results showed that only rats exposed to both food restrictions and stress exhibited BE in the first 15 to 60min after the stressful procedure. Different doses of rhodiola extract were found to either reduce or abolish the BE episode. A stress-induced increase in serum corticosterone levels was also abolished by the herb.[6]

There have been numerous Russian human studies into the effects of rhodiola on endurance, stamina, concentration and fatigue.[7]

A study evaluated the effect of the rhodiola extract, rhodaxon, upon the physical and intellectual working capacity and psychoemotional state of foreign students during their study in a Russian high school. Rhodaxon administration increased the capacity for carrying out physical tasks and also the kinesthetic sensitivity. A marked increase in the general condition and a decrease in the level of mental fatigue and situational anxiety was also observed.[8]

Forty-two master level competitive skiers (20 to 25 years of age) took either rhodiola extract or placebo 30 to 60 minutes before training races (30km) and a biathlon (20km race on skis carrying a rifle and shooting targets at stops). Athletes given rhodiola had statistically significant increased shooting accuracy, less arm tremor and better coordination. Thirty minutes after work performance, the heart rate in the rhodiola group was 104 to 106 percent of baseline, versus 128.7% in the placebo group. Rhodiola improved recovery time, strength, endurance, cardiovascular measures, and coordination.[9]

The stimulating or normalizing effect of the rhodiola extract (SHR-5) in foreign students during a stressful

examination period was studied in a double-blind, randomized and placebo-controlled trial. The SHR-5 extract or placebo were taken for 20 days by the students during an examination period. The physical and mental performance were assessed before and after the period, based on objective as well as on subjective evaluation. The most significant improvement in the SHR-5 group was seen in physical fitness, mental fatigue and neuro-motoric tests. The self-assessment of general well-being was also significantly better in the herbal group. No significance was seen in the correction of text tests or a neuro-muscular tapping test. The overall conclusion found that the rhodiola extract gave significant results compared to the placebo group but that the dose level probably was suboptimal.[10]

The rhodiola extract, SHR-5, was used in another study of individuals suffering from stress-related fatigue. The phase III clinical trial took the form of a randomised, double-blind, placebo-controlled study with parallel groups. A total of 60 individuals (males and females aged between 20 and 55 years) were randomised into two groups. One group received 576mg SHR-5 extract per day while the other group received placebo. The effects of the extract in relation to quality of life, symptoms of fatigue, depression, attention and morning saliva cortisol response were assessed on day 1 and after 28 days of the trial. Significant post-treatment improvements were observed for both groups (placebo effect) in fatigue, mental health, depression and in several indices of attention. When the two groups were compared, however, significant effects of the rhodiola extract compared to placebo were observed in fatigue and attention. Also post-treatment morning cortisol responses were significantly lower in the treatment group compared with the control group.[11]

Another randomized, double-blind, placebo-controlled clinical study examined the effect of two different doses of rhodiola (SHR-5) extract on capacity for mental work against a background of fatigue and stress. Some physiological parameters including pulse rate and blood pressure were also measured. The study was carried out on a highly uniform population comprising 161 cadets aged from 19 to 21 years. All groups were found to have very similar initial data, with no significant difference with regard to any parameter. The study showed a pronounced antifatigue effect for both doses in the treatment groups over placebo. There was a possible trend in favour of the lower dose in the psychometric tests. No such trend was found in the physiological tests.[12]

The same rhodiola extract was used to investigate the effect of repeated low-dose treatment on fatigue during night duty among a group of 56 young, healthy physicians. The effect of the rhodiola extract was measured on mental performance calculated by a Fatigue Index. The tests chosen reflect an overall level of mental fatigue, involving complex perceptive and cognitive cerebral functions, such as associative thinking, short-term memory, concentration and speed of audio-visual perception. These parameters were tested before and after night duty during three periods of two weeks each: a) a test period of one rhodiola/placebo tablet daily, b) a washout period and c) a third period of one placebo/rhodiola tablet daily, in a double-blind cross-over trial. A statistically significant improvement in these tests was observed in the rhodiola treatment group during the first two weeks period. No side-effects were reported for either treatment noted. These results suggest that rhodiola can reduce general fatigue under certain stressful conditions.[13]

Chronic rhodiola supplementation was shown to be able to reduce both lactate levels and parameters of skeletal muscle damage after an exhaustive exercise session. Moreover the rhodiola seemed to ameliorate fatty acid consumption. Taken together these observations confirm that rhodiola may increase the ability to adapt and cope with the stress of physical exercise.[14]

Central Nervous System Activity

Rhodiola has been found to possess both stimulating and relaxing effects on the central nervous system depending on dose. Small to medium doses have been found in early animal studies to be stimulating by increasing the bioelectrical activity of the brain.[15,16] Other studies have found that rhodiola can stimulate various neurotransmitters including dopamine, serotonin and norepinephrine. For example recent studies demonstrated that rhodiola extract could improve serotonin levels in depressive rats and induce neural stem cell proliferation to return to normal level, repairing the injured neurons at hippocampus.[17,18]

Other studies have shown that rhodiola promotes neurotransmitter availability by increasing blood brain permeability to precursors of serotonin and dopamine.[19,20,21] Rhodiola has additionally also been shown to enhance memory by interacting with acetylcholine.[22,23] These combined effects of rhodiola are thought to contribute to the herbs reputation for enhancing learning, concentration, memory and mood.

Rhodiola administration was found to promote a moderate increase in the amount of serum immunoreactive beta-endorphin in rats under basal conditions. The increase is similar to that found when rats are adapted to exercise. When rats were subjected to a 4-hour period of non-specific stress, the expected elevation in beta-endorphin was either not observed or substantially decreased when rhodiola was administered. Consequently, the characteristic perturbations of the HPA were decreased or totally prevented. Rhodiola appeared to have generated non-specific resistance and prepared the rats to respond more appropriately to the eventual stressful situation.[24]

The effect of rhodiola extract on the acquisition and expression of morphine tolerance and dependence in mice was studied. Results showed that the extract significantly reduced the expression of morphine tolerance, while it was ineffective in modulating its acquisition. Conversely, rhodiola significantly and dose-dependently attenuated both the development and expression of morphine dependence after chronic or acute administration suggesting that rhodiola may have human therapeutic potential for treatment of opioid addiction.[25]

Antidepressant and Anxiolytic Activities

There is increasing evidence that prolonged exposure to stressful life events and depression are both related to significant behavioural, endocrinological and neurobiological changes in human and animal subjects. A study examined whether chronic treatment with rhodiola can prevent various physiological and behavioural alterations induced in female rats following 6 weeks of chronic mild stress (CMS). Rats subjected to the CMS procedure demonstrated decreased sucrose intake, reduced moving behaviour, minimized weight gain and dysregulation of their oestrous cycle. Treatment with rhodiola completely reverted all of these changes. The effects were comparable to those of fluoxetine. Interestingly, neither rhodiola nor fluoxetine influence the behavioural and physiological parameters tested in non-stressed animals. These findings strongly showed that chronic administration of rhodiola results in potent inhibition of the behavioural and physiological changes induced by chronic exposure to mild stressors.[26]

A randomized double-blind placebo-controlled study examined the effects of two different doses of rhodiola compared to placebo in patients suffering from a current episode of mild/moderate depression. For individuals taking rhodiola, overall depression, together with insomnia, emotional instability and somatization, but not self-esteem, improved significantly following medication, whilst the placebo group did not show such improvements. No serious side-effects were reported in any of the groups A-C. It was concluded that the rhodiola extract SHR-5 shows antidepressive potency in patients with mild to moderate depression when administered in dosages of either 340 or 680mg/day over a 6-week period.[27]

Rhodiola extract was examined in the prevention of developing nicotine dependence and for the reduction of abstinence suffering following nicotine cessation in mice. Spontaneous abstinence syndrome was evaluated 20 hours after the last nicotine administration, by analysis of withdrawal signs, as affective (anxiety-like behaviour) and physical (somatic signs and locomotor activity). Rhodiola was administered orally during nicotine treatment or during nicotine withdrawal. Both affective and somatic signs (head shaking, paw tremors etc) induced by nicotine withdrawal are abolished by administration of rhodiola in a dose-dependent fashion, during both nicotine exposure and nicotine cessation. Additional studies to define the use of rhodiola as a therapeutic approach in the treatment of smoking cessation are warranted.[28]

The effects produced by a single oral administration of a rhodiola extract on the central nervous system in mice was examined. The extract was tested on antidepressant, adaptogenic, anxiolytic, nociceptive and locomotor activities at different doses using predictive behavioural tests and animal models. The results found rhodiola extract significantly induced antidepressant-like, adaptogenic, anxiolytic-like and

stimulating effects in mice. This study thus provides evidence of the efficacy of rhodiola extracts after a single administration, and confirms many preclinical and clinical studies indicating the adaptogenic and stimulating effects. Antidepressant-like and anxiolytic-like activities of rhodiola were shown in mice for the first time.[29]

Anti-inflammatory Activity

The effects of extracts of Rhodiola rosea radix on blood levels of inflammatory C-reactive protein and creatinine kinase were studied in healthy untrained volunteers before and after exhausting exercise. *Rhodiola rosea* extract exhibited an anti-inflammatory effect and protected muscle tissue during exercise.[30]

The anti-inflammatory efficacy of a rhodiola extract was evaluated in rats - through carrageenan-induced paw oedema, formaldehyde-induced arthritis and nystatin-induced paw oedema. The tincture extract exhibited inhibitory effects against acute and subacute inflammation at a dose of 250mg/kg body weight. Inhibition of nystatin-induced oedema was also observed in a dose-dependent manner.

The inhibitory effects of rhodiola was also evaluated against the enzymes COX-1, COX-2 and Phospholipase A2 (PLA2) relating to inflammation. The extract showed varying inhibitory activities against these enzymes depending on the concentrations. A potent inhibition was observed against Cox-2 and PLA2. Inhibition of nystatin induced oedema and PLA2 suggested that membrane stabilization could be the most probable mechanism of anti-inflammatory action.[31]

The effects of rhodiola on the preventive treatment of acute lung injury (ALI) caused by post-traumatic/ inflammatory and thoracic-cardiovascular operations was studied in 104 patients. Early use of rhodiola was shown to lower the complication rate by around 50% compared to standard care controls. Thus rhodiola was thought to protect against major risk factors of ALI caused by massive trauma/ infection and thoracic-cardio-operations.[32] Another study also found rhodiola to offer good prevention and treatment efficacy in treating complicated acute lung injury during cardiopulmonary bypass in patients with pulmonary hypertension.[33]

Antioxidant Activity

A study found rhodiola extracts reduced oxidative stress through up-regulating reactive oxygen species scavenging capability and enhancing antioxidant defense mechanisms.[34]

Another study found rhodiola extended lifespan in rats through lowering endogenous free radical levels. Researchers found that rhodiola is able to extend the life span of the fruit fly however, the mode of action is currently unknown. Some authors suggested antioxidant actions, whereas others have argued that it may actually be a pro-oxidant and act through a hormetic mechanism. Rhodiola supplementation was found to protect cultured cells against ultraviolet light, paraquat, and hydrogen peroxide. However, it did not alter the levels of the major antioxidant defenses nor did it markedly activate the antioxidant response element. These results suggest that in human cultured cells rhodiola does not act as an antioxidant and that its mode of action cannot be sufficiently explained through a pro-oxidant hormetic mechanism.[36]

Rhodiola had the highest potential for singlet oxygen scavenging, hydrogen peroxide scavenging, ferric reducing, ferrous chelating and protein thiol protection in a study comparing different adapotgens. The antioxidant potential of the adaptogens was found to be proportional to their respective polyphenol content.[37]

Cardioprotective and Antiarrhythmic Activity

Rhodiola extract was found to prevent stress-induced cardiac damage. Myocardial catecholamines and cAMP levels were also measured. Rhodiola was shown to prevent both stress-induced catecholamine release and higher cAMP levels in the myocardium. Moreover, the herb prevented lower adrenal catecholamines during stress. The findings suggest that the antistressor and cardioprotective effects of *Rhodiola rosea* are associated with limited adrenergic effects on the heart.[38]

A course of treatment by Aralia mandshurica or *Rhodiola rosea* extracts reduced the incidence of ischemic and reperfusion ventricular arrhythmias during 10min ischemia and 10min reperfusion. Whereas extracts of *Eleutherococcus senticosus*, *Leuzea carthamoides*, and *Panax ginseng* did not

change the incidence of ischemic and reperfusion arrhythmias. Chronic treatment by Aralia, rhodiola, and *Eleutherococcus* also elevated the ventricular fibrillation threshold in rats with postinfarction cardiosclerosis.[39]

Salidroside, one of the active components of rhodiola shows potent antihypoxia property. The cardioprotective effects of salidroside, from ischemia and reperfusion were examined.

Cardiomyocytes were exposed to 4 hours of ischemia and 16 hours of reperfusion, and then cell viability, apoptosis, glucose uptake, ATP levels and cytosolic Ca(2+) concentration were determined.

Treatment with salidroside markedly improved cell viability, decreased lactate dehydrogenase release, reduced cell apoptosis, significantly improved cardiomyocytes glucose uptake and increased O-linked N-acetylglucosamine GlcNAc levels, as well as reducing cytosolic Ca(2+) concentration compared to untreated cells following ischemia/reperfusion.These results suggested that salidroside significantly decreases cardiomyocyte injury following ischemia/reperfusion.[40]

Another study found salidroside to be protective against cardiomyocyte death or damage. In this study, pretreatment with salidroside markedly attenuated hypoxia-induced cell viability loss, cell necrosis and apoptosis in a dose-dependent manner.[41]

A course injection of rhodiola extract for eight days was reported to increase the resistance of experimental animals to adrenalin or calcium chloride-induced arrhythmias. Preliminary injection of naloxone eliminated the antiarrhythmic effect of rhodiola. The anti-inflammatory drug, indomethacin, had no effect on the antiarrhythmic action of rhodiola. The antiarrhythmic effect of rhodiola was assumed to be associated with the induction of opioid peptides biosynthesis.[42]

Another study found that intravenous infusion of the opioid antagonist, naloxone, completely abolished the favorable effect of rhodiola in relation to the heart contractility and coronary flow parameters. Thus the authors postulated that the protective effect of rhodiola may be connected with an increase in the level of endogenous opioid peptides.[43]

Rhodiola is also a component of the adaptogenic formula Tonizid which has been found to improve cardiac function – through exhibiting cardioprotective and antifibrillatory properties.[44] Tonizid was also found in another study to prevent fibrillation during coronary occlusion and acute cardiac ischemia/reperfusion and postinfarction cardiac fibrosis.[45]

Endocrine and Fertility Activity

Studies in mice and humans have shown that rhodiola can enhance fertility.

One study in mice found that most rhodiola (rhodosin) treated animals had improvements in the number of growing follicles, the oocyte volumes, the accumulation of RNA in oocyte cytoplasm, the proliferation of the lining and glandular cells of the uterine horns, and the preparation of uterine mucosa for fertilization. In sexually mature mice rhodosin increased the mean weight of the uterine horns and the mean weight of the ovaries. However, the administration of rhodosin to sexually immature female white mice for 3 weeks did not affect sexual maturation, the onset of oestrus, the weight of ovaries or uterine horns, or the maturation of follicles.

Thus it is possible that the effects of rhodiola preparations depend upon a specific hormonal interaction with oestrogen receptors.[46]

Forty women with amenorrhea were given rhodiola (either 100mg extract orally twice a day for 2 weeks, or 1mL rhodosin intramuscularly for 10 days). In some subjects the treatment cycle was repeated 2 to 4 times. Normal menses was restored in 25 women, 11 of whom became pregnant. In those with normal menses, the mean length of the uterine cavity increased from 5.5cm to 7.0cm (normal) after rhodiola treatment.[47]

Neuroendocrine animal studies have showed that rhodiola like other adaptogens, enhanced thyroid function without causing hyperthyroidism.[48]

In an open study, 26 out of 35 men with erectile dysfunction and/or premature ejaculation (of 1 to 20 years duration) responded to rhodiola (150 to 200mg/day for 3 months) with substantially improved sexual function, normalization of prostatic fluid, and an increase in 17 ketosteroids in urine.[49]

Immune-Modulating and Anticancer Activity

Rhodiola has been shown to exhibit immunotropic activity in pigs. Blood lymphocyte cultures were found to stimulate or inhibit T cell proliferative responses at different concentrations. The *in vivo* effect of these herbal remedies on the proliferative response of mouse splenic lymphocytes was examined. Significant stimulation of the proliferative response, in comparison to the controls, in mice fed lower doses of tested remedies, and inhibition, no effect or lower stimulation, in mice fed higher doses of rhodiola was demonstrated.[50]

The active constituent from rhodiola, salidroside, was shown to possess immunological adjuvant activity by regulating humoral and cellular immune responses in mice.[51] Administration of *Rhodiola rosea* extract also directly suppressed the growth of and the extent of metastasis from transplanted Lewis lung carcinomas in mice.[52]

Experiments on mice inoculated with metastasing Lewis lung carcinoma showed that the antitumour and antimetastatic effects of cyclophosphan (cyclophosphamide) are potentiated by the extracts of phytopreparations based on baical scullcap (*Scutellaria baikalensis*), rhodiola (*Rhodiola rosea*), common licorice (*Glycyrrhiza glabra*), and their principal acting components – baikalin, paratyrosol, and glycyrram.[53]

In rats with transplanted adenocarcinoma and lymphosarcoma, supplementation with *Rhodiola rosea* extract inhibited the growth of both tumour types, decreased metastasis to the liver and extended survival times.[54]

The anticancer effect of rhodiola on cytostatics, cell cycle, induction of apoptosis or the mitotic activity of healthy and cancerous cells was examined. The extract of rhodiola was found to inhibit division of leukemia cells (HL-60), preceded by an accumulation of cells at the prophase stage. This resulted in an induction of apoptosis and necrosis in HL-60 cells, and to marked reduction of their survival. The cells enter apoptosis from phase G2/M of the cell cycle. After treatment with the extract, no chromosome aberrations or micronuclei were observed, which indicates the mild action of the extract. The cytostatic and antiproliferative effect of the rhodiola extract, and its mild action, suggested possible use in anticancer therapy by enhancing the effectiveness of cytostatics.[55]

The antiviral and immune modulating effects of salidroside, a major component of rhodiola were examined. Salidroside exhibited obvious antiviral effects both in *in vitro* and *in vivo* experiments. Salidroside was found to modulate the mRNA expression of the cytokines interferon-gamma, interleukin-10, tumor necrosis factor-alpha, and interleukin-2. In conclusion, salidroside possesses antiviral activities against CVB3 and it may represent a potential therapeutic agent for viral myocarditis.[56]

Indications

- Physical and emotional stress
- Depression and anxiety
- Endurance and sports
- Cardiovascular disease
- Fatigue
- Poor memory and concentration
- Immune insufficiency and cancer
- Oxidative stress and inflammatory disorders
- Female infertility, sexual dysfunction in men

Energetics

Cool, dry.

Use in Pregnancy

Not known to be contraindicated in pregnancy, though safety studies have not been done.

Contraindications

While the administration of rhodiola may be beneficial in monopolar depression, use is not recommended for bipolar states.

Drug Interactions

Caution with monoamine oxidase inhibitors (MAOIs – used to treat depression), antidepressant (e.g. paroxetine, escitalopram), antidiabetic and immunosuppressant drugs.

Administration and Dosage

Liquid Extract:	1:2
Alcohol:	45%
Weekly Dosage:	15 to 30mL

References

1. Brown RP, Gerbarg PL, Ramazanov Z, Rhodiola rosea: A Phytomedicinal Overview, Herbalgram 2002: 56, p.42.
2. Panossian A, Wikman G, Kaur P, Asea A. Adaptogens exert a stress-protective effect by modulation of expression of molecular chaperones. Phytomedicine. 2009 Jun;16(6-7):617-22.
3. Wiegant FA, Surinova S, Ytsma E, et al, Plant adaptogens increase lifespan and stress resistance in C. elegans. Biogerontology. 2009 Feb;10(1):27-42.
4. Maslov LN, Lishmanov IuB. [Cardioprotective and antiarrhythmic properties of Rhodiolae roseae preparations]. Eksp Klin Farmakol. 2007 Sep-Oct;70(5):59-67.
5. Mattioli L, Perfumi M. Rhodiola rosea L. extract reduces stress- and CRF-induced anorexia in rats. J Psychopharmacol. 2007 Sep;21(7):742-50.
6. Cifani C, Micioni Di B MV, Vitale G, et al, Effect of salidroside, active principle of Rhodiola rosea extract, on binge eating. Physiol Behav. 2010 Dec 2;101(5):555-62
7. Brown RP, Gerbarg PL, Ramazanov Z, Rhodiola rosea: A Phytomedicinal Overview, Herbalgram 2002: 56, p.46
8. Spasov AA, Mandrikov VB, Mironova IA. [The effect of the preparation rodakson on the psychophysiological and physical adaptation of students to an academic load]. Eksp Klin Farmakol. 2000 Jan-Feb;63(1):76-8.
9. Saratikov AS, Krasnov EA. Chapter III: Stimulative properties of Rhodiola rosea. in: Saratikov AS, Krasnov EA. Rhodiola rosea is a valuable medicinal plant (Golden Root). Tomsk, Russia: Tomsk State University; 1987 p. 69-90.
10. Spasov AA, Wikman GK, Mandrikov VB, et.al 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. Phytomedicine. 2000 Apr;7(2):85-9.
11. Olsson EM, von Schéele B, Panossian AG. 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 Feb;75(2):105-12.
12. Shevtsov VA, Zholus BI, Shervarly VI et al, A randomized trial of two different doses of a SHR-5 Rhodiola rosea extract versus placebo and control of capacity for mental work. Phytomedicine. 2003 Mar;10(2-3):95-105.
13. Darbinyan V, Kteyan A, Panossian A et al, 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. Phytomedicine. 2000 Oct;7(5):365-71.
14. Parisi A, Tranchita E, Duranti G et al, Effects of chronic Rhodiola Rosea supplementation on sport performance and antioxidant capacity in trained male: preliminary results. J Sports Med Phys Fitness. 2010 Mar;50(1):57-63.
15. Kurkin VA, Zapesochnaya GG. Chemical composition and pharma- rosea on the human mental activity. Pharmaceutical J 1981; 36(4):62- cological properties of Rhodiola rosea. Chemical and Pharmaceutical 4. Journal (Moscow) 1986; 20(10):1231-44.
16. Saratikov AS, Krasnov EA, Khnikina LA, Duvidson LM. Isolation and chemical analysis of individual biologically active constituents of Rhodiola rosea. Proceedings of the Siberian Academy of Sciences.Biology 1967; 1:54-60.
17. Qin YJ, Zeng YS, Zhou CC, Li Y, Zhong ZQ. [Effects of Rhodiola rosea on level of 5-hydroxytryptamine, cell proliferation and differentiation, and number of neuron in cerebral hippocampus of rats with depression induced by chronic mild stress]. Zhongguo Zhong Yao Za Zhi. 2008 Dec;33(23):2842-6.
18. Chen QG, Zeng YS, Qu ZQ, et al The effects of Rhodiola rosea extract on 5-HT level, cell proliferation and quantity of neurons at cerebral hippocampus of depressive rats. Phytomedicine. 2009 Sep;16(9):830-8.
19. Lazarova MB, Petkov VD, Markovska VL, Petkov VV, Mosharrof A. Effects of meclofenoxate and Extr. Rhodiolae rosea L. on electroconvulsive shock-impaired learning and memory in rats. Methods Find Exp Clin Pharmacol 1986; 8(9):547-52.
20. Petkov VD, Yonkov D, Mosharoff A, Kambourova T, Alova L, Petkov VV, et al. Effects of alcohol aqueous extract from Rhodiola rosea L. roots on learning and memory. Acta Physiol Pharmacol Bulg 1986; 12(1):3-16.
21. Saratikov A, Mar'ina TF, Fisanova LL. Effect of golden root extract on processes of serotonin synthesis in CNS. Journal of Biological Sciences 1978; 6.
22. Mar'ina TF, Alekseeva LP. Effect of Rhodiola rosea extract on electroencephalograms in rabbit. in. Stimulants of the Central Nervous System. Tomsk, Russia: Tomsk State University Press; 1968: 22-6.
23. Mar'ina TF. Effect of Rhodiola rosea extract on bioelectrical activity of the cerebral cortex isolated to a different extent from the brain. Stimulants of the Central Nervous System. Tomsk, Russia: Tomsk State University Press; 1968: 27-31.
24. Lishmanov IB, Trifonova ZV, Tsibin AN, et al. Plasma beta-endorphin and stress hormones in stress and adaptation. Biull Eksp Biol Med 1987;103:422-424.
25. Mattioli L, Perfumi M. Effects of a Rhodiola rosea L. extract on acquisition and expression of morphine tolerance and dependence in mice. J Psychopharmacol. 2011 Mar;25(3):411-20
26. Mattioli L, Funari C, Perfumi M. Effects of Rhodiola rosea L. extract on behavioural and physiological alterations induced by chronic mild stress in female rats. J Psychopharmacol. 2009 Mar;23(2):130-42.
27. Darbinyan V, Aslanyan G, Amroyan E, et al, Clinical trial of Rhodiola rosea L. extract SHR-5 in the treatment of mild to moderate depression. Nord J Psychiatry. 2007;61(5):343-8.
28. Mattioli L, Perfumi M. Evaluation of Rhodiola rosea L. extract on affective and physical signs of nicotine withdrawal in mice. J Psychopharmacol. 2011 Mar;25(3):402-10
29. Perfumi M, Mattioli L. Adaptogenic and central nervous system effects of single doses of 3% rosavin and 1% salidroside Rhodiola rosea L. extract in mice. Phytother Res. 2007 Jan;21(1):37-43.
30. 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 Jul;138(1):63-4.
31. Pooja, Bawa AS, Khanum F. Anti-inflammatory activity of Rhodiola rosea--"a second-generation adaptogen". Phytother Res. 2009 Aug;23(8):1099-102.
32. Zhang S, Gao W, Xu K, et al, [Early use of Chinese drug rhodiola compound for patients with post-trauma and inflammation in prevention of ALI/ARDS]. Zhonghua Wai Ke Za Zhi. 1999 Apr;37(4):238-40.
33. Xu KJ, Zhang SF, Li QX. [Preventive and treatment effect of composite Rhodiolae on acute lung injury in patients with severe pulmonary hypertension during extracorporeal circulation] Zhongguo Zhong Xi Yi Jie He Za Zhi. 2003 Sep;23(9):648-50
34. Huang SC, Lee FT, Kuo TY, Yang JH, Chien CT. Attenuation of long-term Rhodiola rosea supplementation on exhaustive swimming-evoked oxidative stress in the rat. Chin J Physiol. 2009 Oct 31;52(5):316-24.

35. Schriner SE, Abrahamyan A, Avanessian A, et al, Decreased mitochondrial superoxide levels and enhanced protection against paraquat in Drosophila melanogaster supplemented with Rhodiola rosea. Free Radic Res. 2009 Sep;43(9):836-43.
36. Chen TS, Liou SY, Chang YL. Antioxidant evaluation of three adaptogen extracts. Am J Chin Med. 2008;36(6):1209-17.
37. Maslova LV, Kondrat'ev Blu, Maslov LN, et al, [The cardioprotective and antiadrenergic activity of an extract of Rhodiola rosea in stress].
38. Eksp Klin Farmakol. 1994 Nov-Dec;57(6):61-3.
39. Maslov LN, Lishmanov YB, Arbuzov AG et al, Antiarrhythmic activity of phytoadaptogens in short-term ischemia-reperfusion of the heart and postinfarction cardiosclerosis. Bull Exp Biol Med. 2009 Mar;147(3):331-4.
40. Wu T, Zhou H, Jin Z, Bi S, Yang X, Yi D, Liu W. Cardioprotection of salidroside from ischemia/reperfusion injury by increasing N-acetylglucosamine linkage to cellular proteins. Eur J Pharmacol. 2009 Jun 24;613(1-3):93-9
41. Zhang J, Liu A, Hou R et al, Salidroside protects cardiomyocyte against hypoxia-induced death: a HIF-1alpha-activated and VEGF-mediated pathway. Eur J Pharmacol. 2009 Apr 1;607(1-3):6-14.
42. Lishmanov IuB, Maslova LV, Maslov LN, Dan'shina EN. [The anti-arrhythmia effect of Rhodiola rosea and its possible mechanism]. Biull Eksp Biol Med. 1993 Aug;116(8):175-6.
43. Lishmanov IuB, Naumova AV, Afanas'ev SA, Maslov LN. [Contribution of the opioid system to realization of inotropic effects of Rhodiola rosea extracts in ischemic and reperfusion heart damage *in vitro*]. Eksp Klin Farmakol. 1997 May-Jun;60(3):34-6.
44. Arbuzov AG, Krylatov AV, Maslov LN et al, Antihypoxic, cardioprotective, and antifibrillation effects of a combined adaptogenic plant preparation. Bull Exp Biol Med. 2006 Aug;142(2):212-5.
45. Lishmanov IuB, Maslov LN, Arbuzov AG, et al, [Cardioprotective, inotropic, and anti-arrhythmia properties of a complex adaptogen "Tonizid"]. Eksp Klin Farmakol. 2008 May-Jun;71(3):15-22.
46. Gerasimova HD. Effect of Rhodiola rosea extract on ovarian functional activity. Proc. of Scientific Conference on Endocrinology and Gynecology. Sverdlovk, Russia. 1970; 46-8.
47. Saratikov AS, Krasnov EA. Chapter VI: The influence of Rhodiola on endocrine glands and the liver. in: Saratikov AS, Krasnov EA. Rho- diola rosea is a valuable medicinal plant (Golden Root). Tomsk, Rus- sia: Tomsk State University; 1987 p. 180-93.
48. Maslova LV, Kondrat'ev Blu, Maslov LN, Lishmanov IuB. The cardioprotective and antiadrenergic activity of an extract of Rhodiola rosea in stress. Eksp Klin Farmakol 1994; 57(6):61-3.
49. Saratikov AS, Krasnov EA. Chapter VIII: Clinical studies of Rhodiola. in: Saratikov AS, Krasnov EA. Rhodiola rosea is a valuable medicinal plant (Golden Root).Tomsk, Russia: Tomsk State University; 1987 p. 216-27
50. Skopińska-Rózewska E, Sokolnicka I et al, Dose-dependent *in vivo* effect of Rhodiola and Echinacea on the mitogen-induced lymphocyte proliferation in mice. Pol J Vet Sci. 2011;14(2):265-72
51. Guan S, He J, Guo W, et al, Adjuvant effects of salidroside from Rhodiola rosea L. on the immune responses to ovalbumin in mice. Immunopharmacol Immunotoxicol. 2011 Jun 28.
52. Udintsev SN, Schakhov VP. Decrease of cyclophosphamide haematotoxicity by Rhodiola rosea root extract in mice with Ehrlich and Lewis transplantable tumors. Eur J Cancer 1991;27:1182.
53. Razina TG, Zueva EP, Amosova EN, Krylova SG. [Medicinal plant preparations used as adjuvant therapeutics in experimental oncology]. Eksp Klin Farmakol. 2000 Sep-Oct;63(5):59-61.
54. Udintsev SN, Schakhov VP. Decrease of cyclophosphamide haematotoxicity by Rhodiola rosea root extract in mice with Ehrlich and Lewis transplantable tumors. Eur J Cancer 1991;27:1182.
55. Majewska A, Hoser G, Furmanowa M, et al , Antiproliferative and antimitotic effect, S phase accumulation and induction of apoptosis and necrosis after treatment of extract from Rhodiola rosea rhizomes on HL-60 cells. J Ethnopharmacol. 2006 Jan 3;103(1):43-52.
56. 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. Phytomedicine. 2009 Mar;16(2-3):146-55.
57. Kurkin VA, Zapesochnaya GG. Chemical composition and pharmacological characteristics of Rhodiola rosea (review). Journal of Medicinal Plants, Russian Academy of Science, Moscow 1985; 1231-445.