Rhodiola rosea: A Possible Plant Adaptogen

Abstract

Gregory S. Kelly, ND: Rhodiola rosea is a popular plant in traditional medical systems in Eastern Europe and Asia with a reputation for stimulating the nervous system, decreasing depression, enhancing work performance, eliminating fatigue, and preventing high altitude sickness. Rhodiola rosea has been categorized as an adaptogen by Russian researchers due to its observed ability to increase resistance to a variety of chemical, biological, and physical stressors. Its claimed benefits include antidepressant, anticancer, cardioprotective, and central nervous system enhancement. Research also indicates great utility in asthenic conditions (decline in work performance, sleep difficulties, poor appetite, irritability, hypertension, headaches, and fatigue) developing subsequent to intense

physical or intellectual strain. The adaptogenic, cardiopulmonary protective, and central nervous system activities of Rhodiola rosea have been attributed primarily to its ability to influence levels and activity of monoamines and opioid peptides such as beta-endorphins. (Altern Med Rev 2001;6(3):293-302)

Introduction

Rhodiola rosea ("golden root" or "Arctic root") is widely distributed at high altitudes in Arctic and mountainous regions throughout Europe and Asia. It is a popular plant in traditional medical systems in Eastern Europe and Asia, with a reputation for stimulating the nervous system, decreasing depression, enhancing work performance, eliminating fatigue, and preventing high

altitude sickness.1 In addition to Rhodiola rosea, over 200 different species of Rhodiola have been identified and at least 20 are used in traditional medical systems in Asia, including R. alterna, R. brevipetiolata, R. crenulata, R. kirilowii, R. quadrifida, R. sachalinensis, and R. sacra. Rhodiola rosea has been intensively studied in Russia and Scandinavia for more than 35 years. Although the majority of this research on Rhodiola rosea is unavailable for review, available literature is supportive of its adaptogenic properties. Similar to other plant adaptogens investigated by Russian researchers, such as Eleutherococcus senticosus (Siberian ginseng) and Panax ginseng (Korean ginseng), extracts of this plant produce favorable changes in a variety of diverse areas of physiological function, including neurotransmitter levels, central nervous system activity, and cardiovascular function. Rhodiola rosea has been categorized as an adaptogen by Russian researchers due to its observed ability to increase resistance to a variety of chemical, biological, and physical stressors. Origination of the term adaptogen has been dated to 1947 and credited to a Russian scientist, Lazarev. He defined an "adaptogen" as an agent that allows an organism to counteract adverse physical, chemical, or biological stressors by generating non-specific resistance. Inherent in his definition is the concept that administration of the adaptogenic agent allows an organism to pre-adapt itself in a manner that allows it to be more capable of responding appropriately when diverse demands are eventually placed on it. In 1969, Brekhman and Dardymov proposed specific criteria that need to be fulfilled in order for a substance to qualify as an adaptogen. Subjecting animals and humans to a period of stress produces characteristic changes in several hormones and parameters associated with the central nervous system and the hypothalamic-pituitary-adrenal axis (HPA). HPA changes include an increase in cortisol, a reduced sensitivity of the HPA to feedback down-regulation, and a disruption in the circadian rhythm of cortisol secretion. Central nervous system changes include the stress-induced depletion of catecholamine neurotransmitters such as norepinephrine and dopamine. An acute increase in beta-endorphin levels is also observed under stressful conditions. To successfully combat stress and stressful situations, adaptation is required. Adaptation might be best thought of as the ability to be exposed to a stressor, while responding with either decreased or no characteristic hormonal perturbations. Adaptation also implies being prepared to and capable of rapidly reassuming homeostasis after the stressor is withdrawn. As an example, a well-trained athlete can participate in an event that would induce a large HPA perturbation (stress response) in a sedentary person, and yet the athlete will be relatively unaffected. This is a result of adaptation that has occurred during the athlete's training process. Additionally, if athletes are exposed to stressors they were not trained for, hormonal perturbations characteristic of a stress response would be expected; however, this response might not be as great as that found in less fit individuals. Furthermore, after the stress ended, their physiology would be expected to re-establish homeostasis rapidly. This is a result of non-specific resistance to stress gained by virtue of a training-induced higher level of fitness. The utility of plant adaptogens is analogous to the training an athlete undergoes in order to prepare for competition. Plant adaptogens cause our physiology to begin the adaptation process to stress. When a stressful situation occurs, consuming adaptogens generates a degree of generalized adaptation (or non-specific resistance) that allows our physiology to handle the stressful situation in a more resourceful manner. As an example of this process, Rhodiola rosea administration promotes a moderate increase in the amount of serum immunoreactive beta-endorphin in rats under basal conditions. This moderate increase is similar to that found when rats are adapted to exercise. When Rhodiola rosea-treated 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. Consequently, the characteristic perturbations of the HPA were decreased or totally prevented.3 In these rats administration of Rhodiola rosea appears to have generated non-specific resistance and prepared the rats to respond more appropriately to the eventual stressful situation.

Chemical Composition

The chemical composition and physiological properties of Rhodiola species are to a degree species-dependent, although some overlap in constituents and physiological properties does exist in many Rhodiola species. Twenty-eight compounds have been isolated from the roots and above-ground parts of Rhodiola rosea, including 12 novel compounds. The roots contain a range of biologically active substances including organic acids, flavonoids, tannins, and phenolic glycosides. The stimulating and adaptogenic properties of Rhodiola rosea were originally attributed to two compounds isolated from its roots, identified as p-tyrosol and the phenolic glycoside rhodioloside. Rhodioloside was later determined to be structurally similar to the known glycoside salidroside found in several other plant species. Salidroside, rhodioloside, and occasionally rhodosin are used to describe this compound and are considered to be synonyms. Additional glycoside compounds isolated from the root include rhodioniside, rhodiolin, rosin, rosavin, rosarin, and rosiridin. These glycoside compounds are also thought to be critical for the plant's observed adaptogenic properties.1,4 A range of antioxidant compounds have been identified in Rhodiola rosea and related species, including p-tyrosol, organic acids (gallic acid, caffeic acid, and chlorogenic acid), and flavonoids (catechins and proanthocyanidins).5,6 Significant free-radical scavenging activity has been demonstrated for alcohol and water extracts of Rhodiola sp. and is attributed to the variety of antioxidant compounds.5,6 p-Tyrosol has been shown to be readily and dose-dependently absorbed after an oral dose,7,8 and appears to produce a significant antioxidant8 and modest 5-lipoxygenase inhibitory activity9 in vivo. Salidroside (rhodioloside), the additional salidroside-like glycoside compounds (rhodiolin, rosin, rosavin, rosarin, and rosiridin), and p-tyrosol are thought to be the most critical plant constituents needed for therapeutic activity.1,2 The contents of salidroside and p-tyrosol in root samples gathered from various areas in China have been shown to range from 1.3-11.1 mg/g and 0.3-2.2 mg/g, respectively.4 These two compounds have been found in all studied species of Rhodiola; however, the other active glycosides, including rosavin, rosin, and rosarin, have not been found in all examined Rhodiola species.5,6 Because of this variation within the Rhodiola genus, verification of Rhodiola rosea by high performance liquid chromatography (HPLC) is dependent on the content of the additional glycosides (rather than salidroside and p-tyrosol); rosavin is the constituent currently selected for standardization of extracts.10

Proposed Mechanisms of Action

The adaptogenic properties, cardio-pulmonary protective effects, and central nervous system activities of Rhodiola rosea have been attributed primarily to its ability to influence levels and activity of monoamines and opioid peptides such as beta-endorphins. Oral administration of a

water extract of Rhodiola rosea to rats for 10 days modulated biogenic monoamines in the cerebral cortex, brain stem, and hypothalamus. In the cerebral cortex and brain stem, levels of nor-epinephrine and dopamine decreased, while the amount of serotonin increased substantially. In the hypothalamus, the results were reversed with a 3-fold increase in the amount of norepinephrine and dopamine, and a trend toward reduced serotonin levels. It is believed these changes in monoamine levels are a result of Rhodiola rosea inhibiting the activity of the enzymes responsible for monoamine degradation, monoamine oxidase and catechol-O-methyltransferase. It is also believed Rhodiola rosea facilitates the transport of neurotransmitters within the brain.11 In addition to these central effects on monoamines, Rhodiola rosea has been reported to prevent both catecholamine release and subsequent cAMP elevation in the myocardium, and the depletion of adrenal catecholamines induced by acute stress.12 Abstracts of untranslated Russian research indicate that a great deal of the activity of Rhodiola rosea might be secondary to an ability to induce opioid peptide biosynthesis and through the activation of both central and peripheral opioid receptors.3,13-15 Lack of current availability of the complete text of these articles make verification of these effects impossible.

Experimental Studies

Adaptogenic Activity Rhodiola rosea appears to offer generalized resistance against physical, chemical, and biological stressors in rats and other animals studied. Evidence also suggests cardioprotective and anticancer benefits in animals. In the test of swimming "to the limit," Rhodiola rosea administration increased the swimming time of rats 135-159 percent. Working capacity of the rats consistently improved throughout the supplementation period.16 Eggs from the freshwater snail Lymnaea stagnalis were incubated in water extracts of Rhodiola rosea and subsequently exposed to a variety of environmental stressors, including heat shock (43°C for four minutes), oxidative stress (600 µM menadione for two hours), and heavy metal-induced stress (one-hour exposure to 150 µM copper sulphate or 20 µM cadmium chloride). Exposure to these environmental stressors kills 80-90 percent of larvae within four days post-exposure. Pre-incubation with Rhodiola rosea extract afforded a significant degree of non-specific resistance against each of these environmental stressors as measured by rate of survival. While only nine percent of the control population survived exposure to heat shock, approximately 90 percent of snail larvae pre-incubated with Rhodiola rosea (40.5 µg/ml) survived. Pre-incubation with Rhodiola resulted in non-specific resistance to oxidative stress (survival of approximately 68 percent) and heavy metal stress (approximately 28-35 percent of larvae survived depending on the metal exposure).10 Two experiments have suggested possible benefit on various aspects of learning and memory in rats under certain experimental conditions. Rhodiola rosea extract administered orally at a dose of 0.1 mL/day for 10 days resulted in a non-significant trend toward protection against impairments in memory, as assessed by step-down passive avoidance, induced by electroshock in rats.17 Rhodiola rosea extract was administered in a single dose of 0.10 mL. Improvements in both learning and memory retention, as determined by using a maze test with negative reinforcement, were observed. Repeated dosing with the same quantity of the extract over a 10-day period generated significant improvement in long-term memory as assessed by the maze test with negative enforcement and the "staircase" method with positive enforcement. However, in this experiment two other doses were tested (0.02 and

1.0 mL) and were found to have no substantial effect on learning and memory.1 This suggests the possibility of an efficacious dose of Rhodiola rosea administration, above and below which beneficial physiological effects might be less likely. In the other experimental conditions investigated (active avoidance with negative reinforcement using a "shuttle box" and passive avoidance using "step down" and "step through") no beneficial effects on either learning or memory were observed with any of the administered doses of Rhodiola rosea.1 >h3>Cardioprotective Activity Rhodiola rosea has been shown to moderate against stress-induced damage and dysfunction in cardiovascular tissue. Treatment with Rhodiola rosea extract prevents the decrease in cardiac contractile force secondary to environmental stress in the form of acute cooling and contributes to stable contractility. In animals, acute cooling leads to a decrease in myocardial contractile activity that partially recovers during the first 18 hours after the cold-stress is removed. This recovery is viewed as only partial, since the heart tissue is incapable of stable contractility during perfusion. Pretreatment with Rhodiola rosea extracts appears to create a beneficial adaptive response in this type of stress. When Rhodiola pretreated rats were exposed to acute cooling, the decrease in contractility was prevented and stable contractility of heart tissue occurred during perfusion.18 Other reports suggest administration of Rhodiola rosea protects cardiovascular tissue from stress-induced catecholamine release12 and mitigates against adrenaline-induced arrhythmias in rats.13,14,19 The antiarrhythmic effect of Rhodiola rosea is suggested to be secondary to an ability to induce opioid peptide biosynthesis13 and related to the stimulation of peripheral kappa-opioid receptors.14

Anticancer Activity

Administration of Rhodiola rosea appears to have potential as an anticancer agent, and might be useful in conjunction with some pharmaceutical antitumor agents. In rats with transplanted solid Ehrlich adenocarcinoma and metastasizing rat Pliss lymphosarcoma, supplementation with Rhodiola rosea extract inhibited the growth of both tumor types, decreased metastasis to the liver, and extended survival times.20 Administration of Rhodiola rosea extract also directly suppressed the growth of and the extent of metastasis from transplanted Lewis lung carcinomas.21 When Rhodiola rosea extract was combined with the antitumor agent cyclophosphamide in these same tumor models, the antitumor and antimetastatic efficacy of drug treatment was enhanced. The authors also commented that, "complete abrogation of the haematotoxicity of cyclophosphamide" was observed.21 The chemotherapeutic drug Adriamycin is known to induce pronounced liver dysfunction, generally reflected by an increase in transaminase levels. In animal experiments, adding Rhodiola rosea extract to a protocol with Adriamycin resulted in an improved inhibition of tumor dissemination (as compared to that found with Adriamycin alone), and the combined protocol prevented liver toxicity.22

Clinical Studies

Although Rhodiola rosea has been studied in the former Soviet Union for more than 35 years, this research is presently unavailable for review. This makes it impossible to verify the Russian

claims of its antidepressant, anticancer, cardioprotective, and central nervous system enhancing properties.23 Available animal evidence seems supportive of a possible role for this plant adaptogen in many of these conditions. Table 2 outlines the conditions suggested to benefit from Rhodiola supplementation. TABLE 2 * amenorrhea * asthenia * cancer * colds and flu * depression * fatigue * headaches * hypertension * insomnia * schizophrenia * sexual dysfunction (male) There have also been claims that this plant has great utility as a therapy in asthenic conditions (decline in work performance, sleep disturbances, poor appetite, irritability, hypertension, headaches, and fatigue) developing subsequent to intense physical or intellectual strain, influenza and other viral exposures, and other illness. 23 Two randomized, double-blind, placebo-controlled trials of the standardized extract of Rhodiola rosea root (SHR-5) provide a degree of support for these claimed adaptogenic properties and indicate possible utility in asthenic conditions induced by overwork or over study. SHR-5 is standardized to contain rosavin (3.6%), salidroside (1.6%), and p-tyrosol (<0.1%).10 Darbinyan et al evaluated the effect of chronic administration of 170 mg of SHR-5 for 14 days on aspects of mental performance and fatigue on 56 healthy male and female physicians (age 24-35) on night duty. Mental performance was evaluated using tests to determine speed of visual and auditory perception, attention capacity, and short-term memory. Based on the results of the battery of tests used, a Fatigue Index was calculated. The trial was divided into three periods: (1) a two-week test period of one SHR-5 or placebo tablet daily; (2) a two-week washout period; and (3) a third two-week cross-over period of one placebo or SHR-5 tablet daily. A statistically significant improvement in Fatigue Index was observed during the first two-week period in the SHR-5 group, and the improved mental performance reverted toward baseline values during the washout period. Administration of SHR-5 for the final two weeks of the six-week night duty period was unable to significantly offset declines in mental performance.24 Spasov et al investigated the effects of SHR-5 on male medical students during an exam period. Forty students were randomized to receive either 50 mg SHR-5 or placebo twice daily for a period of 20 days. The students receiving the standardized extract of Rhodiola rosea demonstrated significant improvements in physical fitness, psychomotor function, mental performance, and general wellbeing. Subjects receiving the Rhodiola rosea extract also reported statistically significant reductions in mental fatigue, improved sleep patterns, a reduced need for sleep, greater mood stability, and a greater motivation to study. The average exam scores between students receiving the Rhodiola rosea extract and placebo were 3.47 and 3.20, respectively. 25

Dosage and Toxicity

In the two double-blind clinical trials, the dose of a standardized Rhodiola rosea extract ranged from 100-170 mg per day. The content of rosavin consumed in these daily doses is approximately 3.6-6.14 mg. The therapeutic dose of available Rhodiola rosea preparations will vary depending on degree of standardization; however, for chronic administration rosavin content within the above range seems prudent. This would suggest a dose of approximately 360-600 mg Rhodiola rosea daily of an extract standardized for one-percent rosavin, 180-300 mg of an extract standardized for two-percent rosavin, or the dose of between 100-170 mg for an extract standardized for 3.6-percent rosavin. As an adaptogen, chronic administration is normally begun several weeks prior to a period of expected increased physiological, chemical, or biological strain, and continued throughout the duration of the challenging event or activity.

When using Rhodiola rosea as a single dose for acute purposes (e.g., for an exam or athletic competition), the suggested dose is three times the dose used for chronic supplementation. The Russian approach to long-term supplementation with adaptogens generally calls for repeating cycles characterized by short periods of adaptogen administration, followed by an interval with no supplementation.26 Rhodiola rosea has been administered for periods ranging from as little as one day (acute administration) up to four months. Until more specific information is available, a dosing regime following the established patterns used with other plant adaptogens, with periodic intervals of abstinence, seems warranted when Rhodiola rosea is being used chronically. At the doses administered in the clinical trials, a complete absence of all side effects has been reported. However, preliminary clinical feedback indicates that at doses of 1.5-2.0 grams and above of Rhodiola rosea extract standardized for two-percent rosavin, some individuals might experience an increase in irritability and insomnia within several days. It is possible that other physiological parameters that benefit from a lower dose of Rhodiola rosea extract might be exacerbated by a dose that is inappropriately high and/or sustained for prolonged periods of time. Evidence on the safety and appropriateness of Rhodiola rosea supplementation during pregnancy and lactation is currently unavailable.

Conclusion

Consistent with benefits found with other adaptogenic substances, Rhodiola rosea appears to offer generalized resistance to physical, chemical, and biological stressors. Available evidence suggests it can be a suitable substitute in conditions where other adaptogens might be considered. However, Rhodiola rosea also appears to be unique among the currently available adaptogenic herbs and might offer an advantage in some clinical conditions and stressful Circumstances. Unlike Korean and Siberian ginseng, which are thought to exert their adaptogenic activity primarily at the level of HPA function,27-29 Rhodiola rosea appears to exert its adaptogenic effects by working centrally and peripherally on monoamine and opioid synthesis, transport, and receptor activity. If this is in fact the case in humans, it suggests the potential for therapeutic utility of Rhodiola rosea in conditions not particularly responsive to administration of ginseng products. It also suggests the possibility of potential synergistic interactions among Rhodiola rosea and other plant adaptogens. Based on the proposed mechanism of action and available experimental data, Rhodiola rosea appears to offer an advantage over other adaptogens in circumstances of acute stress. A single dose of Rhodiola rosea prior to acute stress produces favorable results and prevents stress-induced disruptions in function and performance. Acute stress tends to initially impact monoamine levels and endorphins, while chronic stress places greater demands on the HPA axis. While this is a generalization and there is obvious overlap in the stress response, Rhodiola does seem to exert a pronounced effect on aspects of the acute stress response. 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 very useful. Rhodiola rosea also offers some cardioprotective benefits not associated with other adaptogens. Its proposed ability to moderate stress-induced damage and dysfunction in cardiovascular tissue might make Rhodiola rosea the adaptogen of choice among patients at higher risk for cardiovascular disease. Since Rhodiola rosea administration appears to impact central monoamine levels, it might also provide benefits and be the adaptogen of choice in

clinical conditions characterized by an imbalance of central nervous system monoamines. This is consistent with Russian claims for improvements in depression and schizophrenia. It also suggests that research in areas such as seasonal affective disorder, fibromyalgia, and chronic fatigue syndrome, to name a few clinical conditions, is warranted. Administration of Rhodiola rosea appears to have potential as an anticancer agent, and might be useful in conjunction with some pharmaceutical antitumor agents. While available evidence is limited to animal models, results appear promising. This is an area that would benefit from additional research. The clearest indication for Rhodiola rosea administration is for the asthenic condition resulting from acute or chronic overwork, which may manifest as decline in work performance, sleep disturbances, poor appetite, irritability, hypertension, headaches, and fatigue. Some animal and preliminary clinical evidence suggests the need for a narrow range of therapeutic dosage of Rhodiola rosea, above and below which beneficial physiological effects might be less likely. Because of this, it seems prudent to keep doses at a moderate level both in terms of the quantity and duration of supplementation. While Rhodiola rosea appears to be a promising plant medicine, and has been investigated intensively in Russia, additional research is required before any conclusions with respect to its therapeutic utility can be made.

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