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Rhodiola rosea: A Versatile Adaptogen

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ABSTRACT: *Rhodiola rosea* (rose root) belonging to the family *Crassulaceae* is a popular medicinal plant in Russia, Scandinavia, and many other countries. Extracts of the roots of this plant have been found to favorably affect a number of physiological functions including neurotransmitter levels, central nervous system activity, and cardiovascular function. It is being used to stimulate the nervous system, decrease depression, enhance work performance, eliminate fatigue, and prevent high-altitude sickness. Most of these effects have been ascribed to constituents such as salidroside (rhodioloside), rosavins, and p-tyrosol. It has also been found to be a strong antioxidant and anticarcinogen due to the presence of several phenolic compounds. Adaptogens are plant extracts that allow an organism to counteract adverse physical, chemical, and biological stressors by generating nonspecific resistance. Adaptogens are known to increase the availability of energy during the day, reduce stressed feelings, increase endurance, and increase mental alertness. This multipurpose medicinal plant (*R. rosea*), with adaptogenic properties that increase the body's nonspecific resistance and normalize functions, has been traditionally grown and used in Russia and Mongolia. Due to increasing consumer demands toward natural health products and the growing interests in the secondary metabolites of plants and their application in biotechnology and therapy, much focus has been put on the rose root and its medical properties. The rose root imparts normalizing influences on adverse physical, chemical, and biological disturbances but is otherwise innocuous. In India, the plant has been growing wild in the high altitudes of the Himalayas. The Defence Research and Development Organization in India has taken on the responsibilities of its conservation, as well as the development of multiple management practices and the development of health foods, supplements, and nutraceuticals in India.

Introduction

Rhodiola rosea belongs to the plant family Crassulaceae, subfamily sedoideae, and genus *Rhodiola* (Linnaeus 1749). *R. rosea* grows primarily in dry sandy ground at high altitudes in the Arctic areas of Europe and Asia (Saratikove and Krasnov 1987). The plant reaches a height of 12 to 30 in (70 cm) and produces yellow flowers. It is a perennial with a thick rhizome and a rose-like fragrance when cut. *R. rosea* has been used in the traditional medicines in Russia, Scandinavia, and other countries.

R. rosea ("golden root," "rose root," or "Arctic root") is widely distributed at high altitudes in the Arctic and mountainous regions throughout the Europe and Asia. It is a popular plant of traditional medical systems in Eastern Europe and Asia, with a reputation of stimulating the nervous system, decreasing depression, enhancing work performance, eliminating fatigue, and preventing high-altitude sickness (Petkov and others 1986). In addition to *R. rosea*, more than 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*.

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R. rosea has been intensively studied in Russia and Scandinavia for more than 35 y. The majority of reports on *R. rosea* are unavailable for review. The 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 roots of *R. rosea* produce favorable changes in a variety of diverse physiological functions, including neurotransmitter levels, central nervous system activity, and cardiovascular function.

Phytochemistry of *R. rosea*

The investigations on the phytochemistry of *R. rosea* root have revealed the presence of about 28 compounds classified into 6 distinct groups (Saratikov and Krasnov 1967; Kurkin and Zapesochnaya 1985):

(1) Phenylpropanoids: rosavin, rosin, rosarin (rosavins is the general term for all 3)
(2) Phenylethanol derivatives: salidroside (rhodioloside), tyrosol
(3) Flavanoids: rodiolin, rodionin, rodiosin, acetylrodalgin, tricin
(4) Monoterpenes: rosiridol, rosaridin
(5) Triterpenes: daucosterol, beta-sitosterol
(6) Phenolic acids: chlorogenic and hydroxycinnamic, gallic acids

According to the Soviet Pharmacopoeia (RFMHMI 1983), the

extracts of *R. rosea*—primarily in the form of water/alcohol tinctures or dried root extract—are now standardized for both rosavins and salidroside. Although rosavins are now the accepted marker for genetically pure *R. rosea* (and its extracts), they are not necessarily the only pharmacologically active ingredients responsible for the efficacy observed in clinical studies. In fact, precise identification of the compounds responsible for the numerous health benefits of *R. rosea* remains to be confirmed. *R. rosea* extracts used in most human clinical studies were standardized to a minimum of 3% rosavins and 0.8% to 1% salidrosides because the naturally occurring ratio of these compounds in *R. rosea* root is approximately 3:1.

Terpenes and aroma volatiles of rhizomes of *R. rosea* L. from Norway have been isolated. The dried rhizomes contained 0.05% essential oil with the main chemical classes: monoterpene hydrocarbons (25.40%), monoterpene alcohols (23.61%), straight-chain aliphatic alcohols (37.54%), n-Decanol (30.38%), geraniol (12.49%), and 1,4-p-menthadien-7-ol (5.10%) were the most abundant volatiles detected in the essential oil, and a total of 86 compounds were identified. Geraniol has been identified as the most important rose-like odorous compound besides geranyl formate, geranyl acetate, benzyl alcohol, and phenylethyl alcohol (Rohloff 2002). Floral notes such as linalool and its oxides, nonanal, decanal, nerol, and cinnamyl alcohol, highlight the flowery scent of rose root rhizomes.

A range of antioxidant compounds have been identified in *R. rosea* and related species, including p-tyrosol, organic acids (gallic acid, caffeic acid, and chlorogenic acid), and flavonoids (catechins and pro-anthocyanidins) by Lee and others (2000) and Ohsugi and others (1999). Significant free-radical scavenging activity has been demonstrated for alcohol and water extracts of *Rhodiola* sp. and is attributed to a variety of antioxidant compounds (Ohsugi and others 1999; Lee and others 2000). p-Tyrosol has been shown to be readily and dose-dependently absorbed after an oral dose and appears to produce a significant antioxidant (Bolshakova and others 1997) and modest 5-lipoxygenase inhibitory activity in vivo. Salidroside (rhodioloside), the additional salidroside-like glycoside compounds (rhodiolin, rosin, rosavin, rosarin, and rosiridin), and p-tyrosol have been believed to be the most critical plant constituents needed for therapeutic activity (Brekhman and Dardymov 1969; Petkov and others 1986). The contents of salidroside and p-tyrosol in root samples gathered from various areas in China have been shown to range from 1.3 mg/g to 11.1 mg/g and from 0.3 mg/g to 2.2 mg/g, respectively (Linh and others 2000). These 2 compounds have been found in all species of *Rhodiola* investigated; however, the other active glycosides, including rosavin, rosin, and rosarin, have not been found in all examined *Rhodiola* species. Because of this variation within the *Rhodiola* genus, verification of *R. rosea* by high-performance liquid chromatography (HPLC) is dependent on the content of the additional glycosides (rather than salidroside and p-tyrosol), and rosavin is the constituent currently selected for standardization of extracts (Boon-Niermeijer and others 2000).

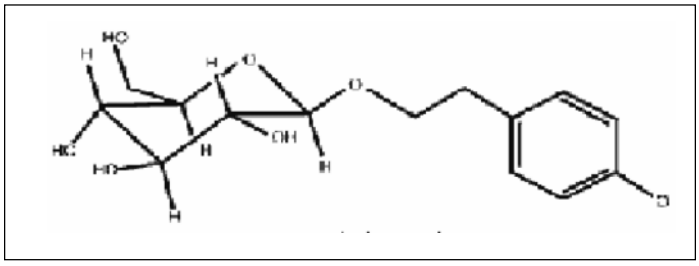

Figure 1—Salidroside.

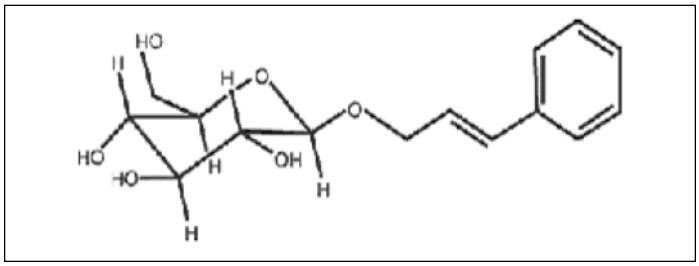

Figure 2—Rosin.

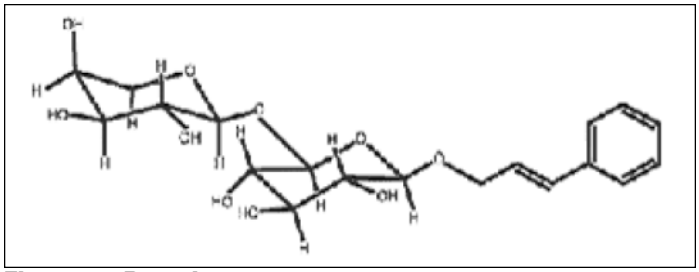

Figure 3—Rosavin.

Applications in Traditional Medicine

Traditionally, the Siberians have used *R. rosea* to increase physical endurance, work productivity, longevity, resistance to high-altitude sickness, and to treat fatigue, depression, anemia, impotence, gastrointestinal ailments, infections, nervous system disorders, cold, flu, tuberculosis, cancer, hernia, leucorrhoea, hysteria, amenorrhea, asthenia, insomnia, schizophrenia, sexual dysfunctions especially in males, headache, scurvy, hemorrhoids, and inflammations. Extracts of the *R. rosea* root have been found to contain powerful adaptogens. Research has revealed that it protected animals and humans against mental and physical stress, toxins, and cold (Krylov 1969; Saratikove and Krasnov 1987). The search for new medicines to treat diseases such as cancer and radiation sickness and to enhance physical and mental performance has led to the discovery of a group of phenylpropanoids that are specific to *R. rosea*.

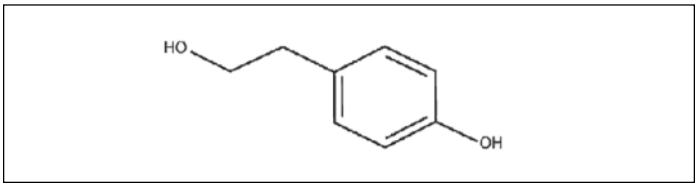

Figure 4—Tyrosol.

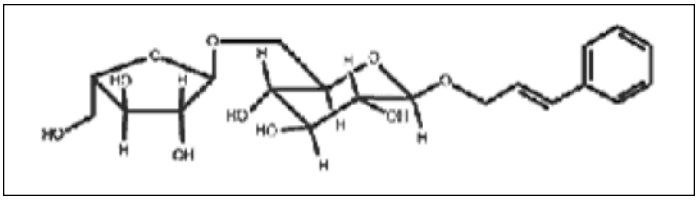

Figure 5—Rosarin.

Table 1—Formulations available in trade

Name Form	Use	Web site	
Neurocalm	Root extract	Positive effects on nervous system, support normal mood	www.symmcorp.com/info/rhodiolarosea.htm
Rhodiola Power	—	Cardiovascular and cerebral health, blood pressure and sugar control, immune support/antifatigue and anti-stress	www.healthkingenterprise.com/rhodiolapower.htm
Anti-aging medicine of 21st century	Dry roots, dry extract, tablets	Anti-aging	www.anti-aging-guide.com/RhodiolaRosea.html
Solary Rhodiola extract	Capsules	Herbal product for natural well-being	www.americanherbalcompany.com/proddetail.cfm
ClearMind	Capsules	Memory, brain tonic	www.iherb.com/rhodiola.html
Protein energizer	Syrup rice protein	For general health, in combination with spirulina, Ginseng,	www.iherb.com/rhodiola.html
Ginza-plus	Liquid gel capsules	In combination with ginseng, Maca, schizandra, cordyceps etc.	www.iherb.com/rhodiola.html
Rhodiola energy (enzymatic therapy)	Capsules	General health, anti-stress	www.iherb.com/rhodiola.html
(T2) planetary formula	Tablets	—	www.iherb.com/rhodiola.html
Arctic roots	Tablets	—	www.iherb.com/rhodiola.html
Rhodiola Now Foods	Vcapsules	—	www.iherb.com/rhodiola.html
Bodyonics	Capsules	—	www.iherb.com/rhodiola.html
Paradise herbs	Capsules	—	www.iherb.com/rhodiola.html
Yellow emperor, rosea extract	Spray bottles	Cognitive stimulant, emotion calming agent	www.yellowemperor.com/theproduct/Liquidextracts
Siberian *Rhodiola* Longevia Rhodiola Rosea formula	Capsules	Anti-aging	www.smartbomb.com/supplements-herb-rhodiola.htm
Vita tonic	Rhodiola extract	Anti-stress, positive mood support and memory-enhacing formula	www.shopping.lycos.co.uk/1915en933.html
Rhodila rosea	Sliced roots formula	Anti-stress, positive mood support, and memory-enhancing naturalelexirstore/longevity/18.htm	www.nutricentre.com/store/
Rhodiola rosea Pinnacle rhodax	— formula	Anti-stress, positive mood support, and memory-enhancing store/pin/rhodax.html	www.bodybuilding.com/

R. rosea in Modern Medicine

Based on the extensive use and beneficial effects of *R. rosea*, the Soviet Ministry of Health in 1975 approved and registered preparation nr 75/933/14 as a medicine and tonic allowing large-scale production under the name Rhodiola Extract Liquid, an alcohol-based extract (40% ethyl alcohol). The common dose was 5 to 10 drops, 2 to 3 times/d, 15 to 30 min before eating for a period of 10 to 20 d. In psychiatric disorders with fatigue, a starting dose of 10 drops, 2 to 3 times/d was gradually increased up to 30 to 40 drops 2 to 3 times/d for 1 to 2 mo. Studies in cell cultures, animals, and humans revealed anti-fatigue, anti-stress, anti-hypoxic (protection against damaging effects of oxygen deprivation), anticancer, antioxidant, immune enhancing, and sexual stimulation effects (Darbinyan and others 2000; Spasov and others 2000).

Effect on the central nervous system

A systematic study of the effects of *R. rosea* revealed that small (100 to 150 mg/d) and medium doses (200 to 600 mg/d) had a simulating effect such as lengthening the time mice could swim and remain on vertical perches to the limit of their abilities. In contrast, larger doses were >600 mg/d) found to have more sedative effects. Small doses increased the bio-electrical activity of the brain, presumably through direct effect on the brain stem ascending and descending reticular formation (Kurkin and Zapesochnaya 1985, 1986; Spasov and others 2000). In short, the effects of *R. rosea* are 2-fold: (1) it stimulated the neurotransmitters such as epinephrine, dopamine, serotonin, and nicotinic cholinergic effects in the central nervous system, and (2) it enhanced the effects of these neurotransmitters on the brain by increasing the permeability of the blood brain barrier to precursors of DA and 5-HT (Saratikov and others 1978; Kurkin and Zapesochnaya 1986; Petkov and others 1986; Petkov and others 1990).

The release of norepinephrine, serotonin, and dopamine in ascending pathways of brain stem activate the cerebral cortex and the limbic system. Consequently, the cognitive (thinking, analyzing, evaluating, calculating, and planning) functions of the cerebral cortex and the attention, memory, and learning functions of the prefrontal and frontal cortex were found to be enhanced. Apart from this, the other neuronal systems such as the cholinergic system use the neurotransmitter acetylcholine (Ach) and contribute to the memory function via pathways ascending from the memory storage in the limbic system to various areas of the cerebral cortex (memory retrieval). Agents that block Ach suppress the activity of these ascending pathways and interfere with memory. *R. rosea* reversed this blockade. The deterioration of these systems with age results in age-associated memory loss (Lupien and others 1998). *R. rosea* may prevent or ameliorate some age-related dysfunction in these neuronal systems.

Stress interferes with memory functions and, over time, causes deterioration in memory systems. *R.. rosea* may exert positive effects on memory and cognition by improving resistance to physi-

cal and emotional stress because the roots of *R. rosea* have been shown to possess antioxidant activity (Durany and others1999; Joseph 1999). Thus, the dual action of cognitive stimulation and emotional calming creates benefits for both immediate cognitive and memory performance and the long-term preservation of brain functions. Krasik and others (1970) have studied the psychostimulant effects of *R. rosea* in 53 healthy subjects and 412 patients with neurosis and asthenic syndromes of both functional and organic origin. Symptoms of asthenia (fatigue, decline in work capacity, falling asleep, poor appetite, irritability, and headaches) responded favorably to *R. rosea* 50 mg 3 times/d. Treatment duration ranged from 10 d to 4 mo. The asthenic states included both psychiatric and physical, for example, following influenza or other illness. In an open study of 128 patients aged 17 to 55 y, *R. rosea* alleviated fatigue, irritability, distractibility, headache, weakness, and other vegetative symptoms in 64% of the cases (Krasik and others 1970). Improvement was assessed by psychological testing and work productivity.

Krasik and others, in another study, have given 27 healthy student, physicians, and scientists, aged 19 to 46 y, 10 drops of *R. rosea* tincture (equivalent to 100 to 150 mg *R. rosea* extract) once or twice per day for 2 to 3 wk, beginning several days before intense intellectual work, such as final exams. The extract was found to improve the amount and quality of work and in all the cases prevented asthenic decompensation (loss of work capacity due to fatigue). The decrease in physical and mental performance of physicians on prolonged night call is well known. A low dose (170 mg/d) of *R. rosea* root extract was given to 56 young, healthy physicians on night call (Darbinyan and others 2000). The effect was measured as total mental performance, calculated as "fatigue index." The tests reflected an overall level of mental fatigue involving complex cognitive functions, such as associative thinking, short-term memory, calculation, concentration, and speed of audio-visual perception. These parameters were tested before and after night duty during 3 periods of 2 wk each in a double-blind crossover trial. A statistically significant improvement in mental performance tests was observed in the treatment group (*R. rosea*) during the 1st 2-wk period. However, at 6 wk, the effect appeared to be lost. No side effects were reported. These results suggest that *R. rosea* root extract can reduce fatigue under certain stressful conditions for some period of time. Possible reasons for the loss of efficacy over the time may be the low dose used, the crossover design, or the overall length of night duty with increased fatigue by weeks 5 and 6.

Changes in neurotransmitter monoamine levels (norepinephrine, dopamine, and serotonin) in nerve tracts involved in the regulation of mood, anxiety, and emotion in the amygdala, hippocampus, hypothalamus, and midbrain may influence emotions. The stimulation of nicotinic cholinergic activity in the emotional circuits of the limbic system (in the temporal lobe) may also contribute to these effects. Alterations in monoamine levels are responsible for this complex spectrum of psychotropic activity: stimulating, tranquilizing, anti-stress, and antidepressant activities.

Effect on physical work capacity

R. rosea has been shown to enhance work capacity and reduce recovery time after exhaustive exercise/physical work. Endurance, which is the capacity to maintain work despite fatigue, is also known to be enhanced by *R. rosea*. In a study at high altitude, a batch of 42 master level skiers were randomly divided into 2 groups before a biathlon (20-km race on skies carrying rifles and shooting targets at stops). One group was given *R. rosea* and another placebo at 1 h before the race. Assessments were made 30 min after the race. The group receiving *R. rosea* had a statistically significant increase in shooting accuracy, less arm tremor, and better coordination, and the heart rate was 104% to 106% of baseline; whereas in the placebo group, the heart rate was about 129% of baseline.

Adaptogens differ from other stimulants during forced, exhaustive muscular work. With classic stimulants, the initial increase in work-capacity is followed by a period of substantially decreased (markedly below average) work capacity. Repeated use of central nervous system stimulants depletes brain catecholamines and decreases conditioned reflexes. In contrast, with extracts of *R.. rosea*, the initial increase in work-capacity is followed by a lesser diminution, such that the work-capacity continues to be above average (Panossian and others 1999).

Animal studies suggest mechanisms that may be involved in these effects. *R. rosea* increased essential energy metabolites, adenosine triphosphate (ATP), and creatine phosphate in the muscle and brain mitochondria of mice made to swim to their limit. It may also enhance the ammonia re-assimilation and energy metabolism of the cell by increasing ATP, ribonucleic acid (RNA), protein, and amino acid synthesis. In animal studies, *R. rosea* increased metabolism of fats twice as much as eleuthero and improved energy metabolism in the brain during intensive muscular workloads.

Adaptogenic and anti-stress effects

R. 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. The origin 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 nonspecific 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 for a substance to qualify as an adaptogen:

(1) An adaptogen should be innocuous and cause minimal disturbance to the normal physiological functions of an organism.

(2) The action of an adaptogen should be nonspecific (that is, it should increase resistance to adverse influences of a wide range of harmful factors of physical, chemical, and or biological nature).

(3) An adaptogen may possess normalizing action irrespective of the direction of the preceding pathological changes (that is, if a body parameter is high, the adaptogen brings it down toward normal; if a parameter is low, the adaptogen pushes/raises it up toward normal).

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 has also been observed under stressful conditions.

Adaptation is required to successfully combat stress and stressful situations. Adaptation might be best thought of as the ability to be exposed to a stressor, while responding with either decreased or uncharacteristic 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 reestablish homeostasis rapidly. This is a result of nonspecific resistance to stress gained by virtue of a training-induced higher level of fitness.

In higher animals and humans, nonspecific resistance may also be enhanced by improvements in the neurological mechanisms dealing with stress (catecholamines, serotonin, and endorphins). The serotonin system is necessary for the stress response reaction, adaptation to new environmental conditions, and tolerance of hypoxia. Numerous stressors decrease serotonin in the hypothalamus. Theoretically, the ability of *R. rosea* to increase the nonspecific resistance of animals may be related to its capacity to increase serotonin in the hypothalamus and midbrain. Additional research showed that an intact HPA axis and participation of the gonads and thymus were necessary for this anti-stress effect. Furthermore, *R. rosea* reduces the activation of several components of the stress response system. For example, it modestly increases serum beta-endorphins that protected rats against subsequent stress-induced excess endorphin elevation (Lishmanov 1987). In addition, *R. rosea* moderates the release of opioid peptides that occurs as part of the HPA axis response to stress. This reduced release protects against sudden excess opioid and catecholamine norepinephrine, dopamine (NE and DA) levels (which interfere with normal brain functions and can lead to heart damage), while allowing a more moderate release that increases stress tolerance without damaging the central nervous system or the cardiovascular system. *R. rosea* extracts also protect the brain and heart by reducing the secretion of corticotrophin-releasing factor (CRF) under stress (Lishmanov 1987).

The main effects of adaptogens are an increased availability of energy during the day, a reduction in stressed feelings, increased endurance, greater mental alertness, and deep and restful sleep. Also, adaptogens significantly accelerate the recovery process after illness. According to modern science, adaptogens are natural plant products that increase the body's ability to cope with internal and external stress factors and normalize the functions of the organism. They help maintain the stable internal environment inside the organism known as homeostasis. An important characteristic is that they are safe, possessing few known side effects.

The adaptogenic properties, cardiopulmonary protective effects, and central nervous system activities of *R. 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 *R. rosea* to rats for 10 d modulated biogenic monoamines in the cerebral cortex, brain stem, and hypothalamus. In the cerebral cortex and brain stem, levels of norepinephrine 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 that these changes in monoamine levels were a result of *R. rosea* inhibiting the activity of the enzymes responsible for monoamine degradation, monoamine oxidase, and catechol-O-methyltransferase. It is also believed that *R. rosea* facilitates the transport of neurotransmitters within the brain (Stancheva and Mosharrof 1987). In addition to these central effects on monoamines, *R. rosea* has been reported to prevent both catecholamine release and subsequent cyclic adenosine monophosphate (cAMP) elevation in the myocardium, and the depletion of adrenal catecholamines induced by acute stress.

In the 2 double-blind clinical trials, the dose of a standardized *R. rosea* extract ranged from 100 mg/d to 170 mg/d. The content of rosavin consumed in these daily doses was approximately 3.6 mg to 6.14 mg. The therapeutic dose of available *R. rosea* preparations varied, depending on degree of standardization; however, for chronic administration, rosavin content within the above range was found to be prudent. This suggested a dose of approximately 360 to 600 mg *R. rosea* daily of an extract standardized for 1% rosavin, 180 to 300 mg of an extract standardized for 2% rosavin, or a dose of between 100 to 170 mg for an extract standardized for 3.6% rosavin. As an adaptogen, chronic administration is normally begun several weeks before a period of expected increased physiological, chemical, or biological strain, and continued throughout the duration of the challenging event or activity. When using *R. rosea* as a single dose for acute purposes (for example, for an exam or athletic competition), the suggested dose is 3 times the dose used for chronic supplementation.

Based on the proposed mechanism of action and available experimental data, *R. rosea* appears to offer an advantage over other adaptogens in circumstances of acute stress. A single dose of *R. rosea* before acute stress produces favorable results and prevents stress-induced disruptions in function and performance. Acute stress tends to initially impact monoamine levels and endorphins, whereas chronic stress places greater demands on the HPA axis. *Rhodiola* does seem to exert a pronounced effect on aspects of the acute stress response. Because 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.

Phases in stress progression

Hans Seyle (father of modern stress theory) was able to demonstrate that under normal conditions, the body is able to use its homeostatic (self-regulatory system) mechanisms to counter various stresses. However, these same mechanisms could be overwhelmed by too much stress. The person would then start to develop various symptoms associated with burnout. Combined or sustained minor stresses, each incapable of triggering an alarm reaction in the general adaptation syndrome, can produce an all-out alarm response and lead to burnout. The general adaptation syndrome (GAS) is divided into 3 phases:

(1) Fight or flight, alarm phase. This response is an alarm reaction triggered by messages in the brain. The pituitary gland releases adrenocorticotropic hormone (ACTH). ACTH causes the adrenal glands to secrete adrenaline, cortisol, and other stress hormones. The heart beats faster to provide blood to the muscles and brain. The breath rate increases to supply extra oxygen to the muscles, heart, and brain. Digestion and other functions not essential for maintaining the alarm reaction are halted. The liver rids itself of stored glycogen and releases glucose into the bloodstream. The body is now ready for any real or imagined danger.

(2) Adaptation phase. If the stress factor continues (for example, in sport it might be heavy athletic training), our body learns to tolerate the stressful stimulus—"adapt"—and increase its resistance to the stress factor. The adaptation phase is usually a safe period and allows the body to endure ongoing stress. The longer we can stay in the adaptation phase, the better.

(3) Exhaustion phase. In this phase, the body fails to fight stress anymore and simply gives up. This stage is a result of chronic oversecretion of cortisol. This leads to adrenal exhaustion. Adrenal exhaustion accelerates the downward spiral to chronic poor health. Chronic headaches, nausea, allergies, nagging injuries, fatigue, dizziness, hypotension, low body temperature, depression, low sex drive, chronic infections, and cold hands and feet are just some of the symptoms that occur with adrenal exhaustion.

Diseases associated with stress may appear in the 1st alarm phase, but they mainly appear in the 3rd exhaustion phase when the body cannot fight stress anymore. This 3rd phase usually develops after a period of months or years. Everything depends on

the duration of the adaptation phase. Sometimes the body may be fortunate enough to escape the 3rd phase altogether, provided it can keep the stress under control. It is possible to do this by taking adaptogens; they can help you to stay in the adaptation phase for as long as possible. *R. rosea* leads to an increase in the amount of basic β-endorphin in the blood plasma, which inhibits the hormonal changes indicative of stress.

Effect on learning and memory

Studies have suggested possible benefits in various aspects of learning and memory in rats under certain experimental conditions. *R. rosea* extract administered orally at a dose of 0.1 mL/d for 10 d resulted in a nonsignificant trend toward protection against impairments in memory, as assessed by step-down passive avoidance, induced by electric shock in rats (Lazarova and others 1986). In another study, *R. rosea* extract was administered in a single dose of 0.10 mL. Improvements in both learning and memory retention, as determined by a maze test with negative reinforcement, were observed. Repeated dosing with the same quantity of the extract over a 10-d 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, 2 other doses were tested (0.02 and 1.0 mL) and were found to have no substantial effect on learning and memory (Petkov and others 1986).

Effect on endocrine and reproductive activity

Animal studies have shown that *R. rosea* enhanced thyroid function without causing hyperthyroidism, an action similar to other adaptogen. Rhodiola rosea is known to improve the thyroid functions such as helping the body utilize energy well, stay warm, and keep brain, heart, muscles and other organs working at their best. In addition, the adrenal gland functioned with better reserve and without the kind of hypertrophy caused by other psychostimulants. Egg maturation was enhanced in rats, and an anabolic effect in males (increased muscle building and gonad strengthening similar to the effect of low-dose testosterone) was observed in a number of species. Administration of rhodosin (extract of *R. rosea* for intravenous, intramuscular, or peritoneal injection) to sexually mature female mice over a period of 4 wk prolonged menstruation from 1.3 d (control) to 2.8 d (rhodosin treated), reduced the resting period from 3.8 d (control) to 2.2 d (rhodosin treated), and increased the relative number of estrus days from 29% to 56%. In the majority of rhodosin-treated animals, 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 increased. In sexually mature mice, rhodosin increased the mean weight of the uterine horns from 39.6 ± 4.11 mg to 59.5 ± 1.59 mg and the mean weight of the ovaries from 6.4 ± 0.65 mg to 9.1 ± 0.45 mg. However, the administration of rhodosin to sexually immature female white mice for 3 wk did not affect sexual maturation, the onset of estrus, the weight of ovaries or uterine horns, or the maturation of follicles. Thus, it is probable that the estrogenic effects of *R. rosea* preparations depend on the specific hormonal milieu (Gerasimova 1970).

These pre-clinical investigations led to a study on the role of *R. rosea* extract in women suffering from amenorrhea (loss of menstrual cycles). Forty women with amenorrhea were given *R. rosea* (either 100 mg extract orally twice a day for 2 wk, or 1 mL rhodosin intramuscularly for 10 d). In some subjects, the treatment cycle was repeated 2 to 4 times. Normal menses were restored in 25 women, 11 of whom became pregnant. In those with normal menses, the mean length of the uterine cavity increased from 5.5 cm to 7.0 cm (normal) after *R. rosea* treatment (Gerasimova 1970). In an open study, 26 of 35 men with erectile dysfunction and/or premature ejaculation (of 1- to 20-y duration) responded to *R. rosea* (150 to 200 mg/d for 3 mo) with substantially improved sexual function, normalization of prostatic fluid, and an increase in 17-ketosteroids in urine.

Cardioprotective effects

Cardioprotective effects of *R. rosea* include prevention of stress-induced cardiac damage (Lishmanov and others 1987); decreased myocardial catecholamines and cAMP levels; and reduced adrenal catecholamine release (Lishmanov and others 1987). Furthermore, *R. rosea* activation of mu-opiate receptors in animal heart muscles prevented re-perfusion arrhythmias. This effect could be blocked by naloxone injection (known to inhibit mu-opiate receptors), thus confirming that the anti-arrhythmic effect of *R. rosea* is associated with the mu-opiate receptors in myocardial (heart) muscle.

Both the sympathetic and parasympathetic inputs to the heart were enhanced such that the heart showed increased reserves under stress of greater intensity. The autonomic nervous system controls automatic or involuntary functions of the body. It has 2 components: the sympathetic and the parasympathetic nerves. The sympathetic nervous system is the "fight-or-flight" system that helps the organism respond to stress (for example, by increasing heart rate, respiratory rate, and muscle tone). The parasympathetic nervous system conserves and restores energy (for example, by slowing the heart rate, respiratory rate, and metabolism). By enhancing the functions of the sympathetic and parasympathetic systems, *R. rosea* enables the organism to put out more energy during stress while at the same time maintaining higher energy reserves. One of the challenges presented by research on a multi-ingredient formula is that it is not usually possible to attribute the results to the activity of any 1 single herbal component. However, the results of this study are consistent with those of others conducted solely on *R. rosea* mono-preparations.

In a Russian study, an extract of *R. rosea* was examined for its effects on the pattern of stress-induced cardiac damage, which was measured by enzyme accumulation in the heart. *R. rosea* was found to prevent stress-induced cardiac damage. Simultaneously, the extract was determined to prevent both stress-induced release of proteins and higher enzyme levels, which can ultimately damage heart tissue. The findings suggested antistressor and cardioprotective benefits of *R. rosea* without any harmful effects on the heart.

Antioxidant and anticarcinogenic effect

R. rosea is rich in phenolic compounds, known to have strong antioxidant properties. Animal studies have shown that *R. rosea* decreases toxicity from cyclophosphamide, rubomycin, and adriamycin (anti-cancer drugs), while it enhances their anticarcinogenic effects. Udintsev and Schakhov (1991) studied the effect of *R. rosea* root extract (RRRE), a tincture manufactured according to the Russian Pharmacopoeia standards (minimum 0.8% salidroside and 3% rosavin) on tumor cells (transplanted into mice) and normal bone marrow cells in 2 mouse cancer models (Udintsev and Schakhov 1991). One group of mice with Ehrlich ascites tumor (EAT) and another group with Lewis lung carcinoma (3LL) were 1st treated with 100 mg/kg cyclophosphamide (a chemotherapy agent) that suppressed tumor growth 31% to 39% and limited 3LL metastases 18%, while also reducing the number of normal bone marrow cells, leukocytes, and myelokariocytes to 40% to 50% and 20% to 25% of normal, respectively. In comparison, RRRE, 0.5 mg/kg/d given orally 2 to 8 d after tumors had been transplanted, suppressed the growth of both tumors (by 19% to 27%) and 3LL metastases (by 16%). However, in contrast to cyclophosphamide, RRRE caused no reduction in normal bone marrow cells. In animals given both RRRE and cyclophospha-

mide, the RRRE increased the antimetastatic effect of cyclophosphamide by 36% ($P < 0.05$).

Many chemotherapy agents are hematotoxic (reduce the number of normal blood cell precursors in bone marrow) or hepatotoxic (cause damage to the liver). These serious side effects were significantly ameliorated by RRRE. Thus, the research suggests that RRRE can both enhance tumor inhibition by chemotherapeutic drugs and alleviate dangerous side effects.

Substances that reduce the incidence of chromosomal aberrations are termed antimutagenic. Salikhova and others (1997) found that in mice injected with cyclophosphamide, RRRE (minimum 0.8% salidroside and 3% rosavin) had antimutagenic effects. Compared with placebo controls, RRRE reduced the development of chromosomal aberrations by 50% and incidence of cells with micronuclei by more than 50%. RRRE also increased indices of DNA repair in bone marrow cells after exposure to the mutagen N-nitroso-N-methyl urea (NMU).

In a small pilot study of 12 patients with superficial bladder carcinoma (TIG1-2), treatment with RRRE (minimum 0.8% salidroside and 3% rosavin) improved parameters of leukocyte integrines and T-cell immunity. The average frequency of relapse was reduced but did not reach statistical significance. Larger placebo-controlled studies of *R. rosea* extracts to augment tumor inhibition and reduce toxic effects of chemotherapy agents are needed.

Toxicity, contraindications, and side effects

R. rosea has a very low level of toxicity. In rat toxicity studies, the LD_{50} (lethal dose at which 50% of animals die) was calculated to be 28.6 mL/kg, approximately 3360 mg/kg (Kurkin and Zapesochnaya 1985). The equivalent dosage in a 70-kg man would be about 235 g or 235000 mg. Because the usual clinical doses are 200 to 600 mg/d, there is a huge margin of safety (Udintsev and Schakov 1991).

Overall, *R. rosea* has very few side effects. Most users find that it improves their mood, energy level, and mental clarity. Some individuals, particularly those who tend to be anxious, may feel overly activated, jittery, or agitated. If this occurs, then a smaller dose with very gradual increases may be needed. *R. rosea* should be taken early in the day because it can interfere with sleep or cause vivid dreams (not nightmares) during the 1st few weeks. It is contraindicative in excited states. Because *R. rosea* has an activating antidepressant effect, it should not be used in individuals with bipolar disorder, who are vulnerable to becoming manic when given antidepressants or stimulants. The herb does not appear to interact with other medications, although it may have additive effects along with other stimulants. It is best absorbed when taken on an empty stomach at 30 min before breakfast and lunch. As with any herbal preparation, patients should inform their primary health care practitioner when taking *R. rosea*.

Conclusions

More scientific research is needed to confirm the preventive and curative benefits of *R. rosea*. Controlled studies are warranted to explore its use in antidepressant augmentation, disorders of memory and cognition, attention deficit disorder, traumatic brain injury, Parkinson's disease, protection against arrhythmias, sports performance, aviation and space medicine (enhancing physical and mental performance while reducing stress reactions), endocrine disorders (infertility, premenstrual disorder, menopause), sexual dysfunction, disorders of the stress-response system (fibromyalgia, chronic fatigue syndrome, and posttraumatic stress disorder), and enhancement of chemotherapy/radiation with amelioration of toxicity.

During evolution, *R. rosea* has adapted to the harsh conditions of high altitude (extreme cold, low oxygen, little rainfall, and intense irradiation from the sun) by producing a group of powerful protective compounds that have diverse beneficial effects in animals and humans. One is struck by the versatility of *R. rosea*, from its description in Greek medicine 2000 y ago to its use by 21st-century cosmonauts. It is time for modern research, using controlled clinical trials, to develop the potential medical applications for this unique phyto-adaptogen. There is immense potential to develop health foods, foods supplements, herbal preparations, and drugs from this unique herb from high altitudes. Its potential for development of radioprotectants—needed in today's world—is immense. Promotion of its production and protection would be beneficial to society.

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References

Bolshakova IV, Lozovskaia EL, Sapezhinskii II. 1997. Antioxidant properties of a series of extracts from medicinal plants. Biofizika 42(2):480–3.

Boon-Niermeijer EK, van den Berg A, Wikman G, Wiegant FA. 2000. Phyto-adaptogens protect against environmental stress-induced death of embryos from the freshwater snail *Lymnaea stagnalis*. Phytomedicine 7(5):389–99.

Brekhman II, Dardymov IV. 1969. New substances of plant origin which increase nonspecific resistance. Ann Rev Pharmacol 9:419–30.

Darbinyan V, Kteyan A, Panossian A, Gabrielian E, Wikman G, Wagner H. 2000. *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 7(5):365–71.

Durany N, Munch G, Michel T, Riederer P. 1999. Investigations on oxidative stress and therapeutical implications in dementia. Eur Arch Psych Clin Neurosci 249(Suppl 3):68–73.

Gerasimova HD. 1970. Effect of *Rhodiola rosea* extract on ovarian functional activity. Proc of Scientific Conference on Endocrinology and Gynecology; Sverdlovsk, Russia; 1970 Sept 15–6. Siberia, Russia: Siberian Branch of the Russian Academy of Sciences. p 46–8.

Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ, and Bickford PC. 1999. Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. J Neurosci 19(18):8114–21.

Krasik ED, Morozova ES, Petrova KP, Ragulina GA, Shemetova LA, Shuvaev VP. 1970. Therapy of asthenic conditions: clinical perspectives of application of *Rhodiola rosea* extract (golden root). In: Proceedings modern problems in psychopharmacology. Kemerovo, Russia; 27-9 May 1070; Siberian Branch of Russian Academy of Sciences. p 298–330.

Krylov GV. 1969. Herbs for Life. Novosibirsk, Russia: Academic Press. p 264.

Kurkin VA, Zapesochnaya GG. 1985. Chemical composition and pharmacological characteristics of *Rhodiola rosea* [review]. J Med Plants (Moscow) 1985:1231–445.

Kurkin VA, Zapesochnaya GG. 1986. Chemical composition and pharmacological properties of *Rhodiola rosea*. Chem Pharm J (Moscow) 20(10):1231–44.

Lazarova MB, Petkov VD, Markovska VL, Petkov VV, Mosharrof A. 1986. Effects of meclofenoxate and extr. *Rhodiolae rosea* L. on electroconvulsive shock-impaired learning and memory in rats. Meth Find Exp Clin Pharmacol 8(9):547–52.

Lee MW, Lee YA, Park HM, and Roh SH, Lee EJ, Jang HD, Kin YH. 2000. Antioxidative phenolic compounds from the roots of Rhodiola sachalinensis A. Bor Arch Pharm Res 23:455–8.

Linh PT, Kim YH, Hong SP, Jian JJ and Kang JS. 2000. Quantitative determination of salidroside and tyrosol from the underground part of *Rhodiola rosea* by high performance liquid chromatography. Arch Pharm Res 23:349–52.

Linnaeus C. 1749. Materia medica. Liber I. De plantis. Stockholm: Lars Salvius. p 168.

Lishmanov IB, Trifonova ZV, Tsibin AN, Maslova LV, Dementeva LA. 1987. Plasma beta-endorphin and stress hormones in stress and adaptation. Bull Eksp Biol Med 103(4):422–4.

Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, Thakur M, McEwen BS, Hanger RL, and Meaney MJ. 1998. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat Neurosci 1(1):69–73.

Ohsugi M, Fan W, Hase K, Xiang Q, Tezuka Y, Komatsu K, Namba T, Saitoh T, Tazawa K and Kadota S. 1999. Active-oxygen scavenging activity of traditional nourishing-tonic herbal medicines and active constituents of Rhodiola sacra. J Ethnopharmacol 67:111–9.

Panossian A, Wikman G, Wagner H. 1999. Plant adaptogens. III. Earlier and more recent aspects and concepts on their mode of action. Phytomedicine 6(4):287–300.

Petkov VD, Stancheva SL, Tocuschieva L, Petkov VV. 1990. Changes in brain biogenic monoamines induced by the nootropic drugs adafenoxate and meclofenoxate and by citicholine (experiments on rats). Gen Pharmacol 21(1):71–5.

Petkov VD, Yonkov D, Mosharoff A, Kambourova T, Petkov VV, and Todorov I. 1986. Effects of alcohol aqueous extract from *Rhodiola rosea* L. roots on learning and memory. Acta Physiol Pharmacol Bulg 12(1):3–16.

Rohloff J. 2002. Volatiles from rhizomes of *Rhodiola rosea* L. Phytochemistry

59:655–66.
[RFMHMI] Russian Federation Ministry of Health and Medical Industry. 1983. PA 42-2126-83, liquid extract of *Rhodiola rosea* root and rhizome. Moscow: The Russian Federation Ministry of Health and Medical Industry, Russian Natl. Pharmacopoeia.
[RFMHMI] Russian Federation Ministry of Health and Medical Industry. 1989. Moscow: The Russian Federation Ministry of Health and Medical Industry, Russian Natl. Pharmacopoeia.
Salikhova RA, Aleksandrova IV, Mazurik VK, Mikhailov VF, Ushenkova LN, Poroshenko GG. 1997. Effect of *Rhodiola rosea* on the yield of mutation alterations and DNA repair in bone marrow cells. Patol Fiziol Eksp Ter 4:22–4.
Saratikov A, Marina TF, Fisanova LL. 1978. Effect of golden root extract on processes of serotonin synthesis in central nervous system. J Biol Sci (8)6:142.
Saratikov AS, Krasnov EA, Khnikina LA, Duvidson LM. 1967. Isolation and chemical analysis of individual biologically active constituents of *Rhodiola rosea*. Proc Siberian Acad Sci Biol 1:54–60.
Saratikov AS, Krasnov EA. 1987. *Rhodiola rosea* is a valuable medicinal plant (Golden Root). Tomsk, Russia: Tomsk State Univ. Press.
Spasov AA, Wikman GK, Mandrikov VB, Mironova IA, Neumoin VV. 2000. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of *Rhodiola rosea* SHR-5 extract on the fatigue of student caused by stress during an examination period with a repeated low-dose regimen. Phytomedicine 7(2):85–9.
Stancheva SL, Mosharrof A. 1987. Effect of the extract of *Rhodiola rosea* L. on the content of the brain biogenic monoamines. Med Physiol Comp Rend Acad Bulg Sci 40(6):85–7.
Udintsev SN, Schakhov VP. 1991. Decrease of cyclophosphamide haematotoxicity by *Rhodiola rosea* root extract in mice with Ehrlich and Lewis transplantable tumors. Eur J Cancer 27(9):1182.
Visioli F, Galli C, Bornet F, Mattei A, Patellir, Galli G, Caruso D. 2000. Olive oil phenolics are dose dependently absorbed in humans. FEBS Lett 468:159–60.