Rhodiola rosea:
A Phytomedicinal Overview

by

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Rhodiola rosea L., also known as "golden root" or "roseroot" belongs to the plant family Crassulaceae.[1] *R. rosea* grows primarily in dry sandy ground at high altitudes in the arctic areas of Europe and Asia.[2] The plant reaches a height of 12 to 30 inches (70cm) and produces yellow blossoms. It is a perennial with a thick rhizome, fragrant when cut. The Greek physician, Dioscorides, first recorded medicinal applications of *rodia riza* in 77 C.E. in *De Materia Medica*.[3] Linnaeus renamed it *Rhodiola rosea*, referring to the rose-like attar (fragrance) of the fresh cut rootstock.[4]

For centuries, R. rosea has been used in the traditional medicine of Russia, Scandinavia, and other countries. Between 1725 and 1960, various medicinal applications of *R. rosea* appeared in the scientific literature of Sweden, Norway, France, Germany, the Soviet Union, and Iceland.[2,4-12] Since 1960, more than 180 pharmacological, phytochemical, and clinical studies have been published. Although R. rosea has been extensively studied as an adaptogen with various health-promoting effects, its properties remain largely unknown in the West. In part this may be due to the fact that the bulk of research has been published in Slavic and Scandinavian languages. This review provides an introduction to some of the traditional uses of R. rosea, its phytochemistry, scientific studies exploring its diverse physiological effects, and its current and future medical applications.

Rhodiola rosea in Traditional Medicine

Traditional folk medicine 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, and nervous system disorders. In mountain villages of Siberia, a bouquet of roots is still given to couples prior to marriage to enhance fertility and assure the birth of healthy children.[2] In Middle Asia, *R. rosea* tea was the most effective treatment for cold and flu during severe Asian winters. Mongolian doctors prescribed it for tuberculosis and cancer.[13] For centuries, only family members knew where to harvest the wild "golden roots" and the methods of extraction.[2] Siberians secretly transported the herb down ancient trails to the Caucasian Mountains where it was traded for Georgian wines, fruits, garlic, and honey. Chinese emperors sent expeditions to Siberia to bring back the "golden root" for medicinal preparations.

Linnaeus wrote of *R. rosea* as an astringent and for the treatment of hernia, leucorrhoea (vaginal discharge), hysteria, and headache.[4,7] In 1755 *R. rosea* was included in the first Swedish Pharmacopoeia. Vikings used the herb to enhance their physical strength and endurance.[14] German researchers described the benefits of *R. rosea* for pain, headache, scurvy, hemorrhoids, as a stimulant, and as an anti-inflammatory.[15,16]

In 1961, G.V. Krylov, a Russian botanist and taxonomist in the Department of Botany at the Novosibirsk Branch of the Russian Academy of Sciences, led an expedition to the cedar taiga in the Altai Mountains of southern Siberia where he located and identified the "golden root" as *Rhodiola rosea*.[17] Extracts of the *R. rosea* root were found to contain powerful adaptogens. Research revealed that it protected animals and humans from mental and physical stress, toxins, and cold.[2,17] The quest for new medicines to treat diseases such as cancer and radiation sickness, and to enhance physical and mental performance, led to the discovery of a group of phenylpropanoids that are specific to *R. rosea*. (See Phytochemistry section below.)

Geographical Distribution and Taxonomy of Rhodiola rosea

While *Rhodiola* as a genus may have originated in the mountainous regions of Southwest China and the Himalayas,[18] botanists have established that various species of the genus *Rhodiola* naturally display a circumpolar distribution in mountainous regions in the higher latitudes and elevations of the Northern Hemisphere. In Central and Northern Asia, the genus is distributed from the Altai Mountains across Mongolia into many parts of Siberia.[19] According to Hegi, its distribution in Europe extends from Iceland and the British Isles across Scandinavia as far south as the Pyrenees, the Alps, the Carpathian Mountains and other mountainous Balkan regions. Several varieties of *Rhodiola* species have also been identified across Alaska, Canada, and the northern mountains of the continental United States.[20] In fact, the world database of botanical literature shows many citations identifying a broad range of species of the genus *Rhodiola*, in some cases including *R. rosea*, in many diverse locations in northern latitudes (see Table 1).

The current taxonomical status of the genus *Rhodiola* has become quite complex. Before World War II, some taxonomists separated different species of *Rhodiola* into an independent genus, belonging to the subfamily *Sedoidae*.[20] Then *Rhodiola* was reclassified as a subgenus of the larger genus *Sedum*, which contained about 10 species. In 1963 Hegi identified more than 50 species of *Rhodiola* and re-established them as a separate genus.[20] Due to their morphological similarities, they form a distinct *Rhodiola* group.[21] There are still differing opinions among specialists about which new species should or should not be included in the genus *Rhodiola*. The rationale and defining criteria for the boundaries of the genus remain somewhat controversial. This is not, in itself, necessarily counterproductive, since the acquisition of botanical knowledge inevitably stimulates new understanding and insight, creating the need for revised systems of classification. In the case of *R. rosea*, however, this taxonomic ambiguity may have unexpected and potentially negative consequences.

Popularizing a phytomedicinal plant like *R. rosea* can create confusion when the public is offered a variety of "*Rhodiola*" products using the general plant family name instead of the full botanical name of the particular species. For example, products called "*Rhodiola* spp., Tibetan *Rhodiola* or Indian *Rhodiola*" may incorrectly imply equivalence with *R. rosea* extract. Because of significant species-dependent variation in phytochemistry and pharmacology, the use of "*Rhodiola*" as a general term is inaccurate and misleading. The correct identification of all *Rhodiola* species according to precise and generally accepted botanical, phytochemical, and genetic taxonomic criteria is not merely an abstract intellectual exercise. It is critical for both scientific and phytopharmacological accuracy, as well as for product labeling for the public. Consumers may need professional guidance to avoid

purchasing ineffective brands, particularly those that do not provide full information, including the complete botanical name of the plant species. Companies may change their suppliers over time. Therefore, consumers should periodically check independent sources of product evaluation, as well as requesting information about quality control and content from manufacturers.

The pharmacological and medicinal properties of *Rhodiola* are species-dependent phenomena.[22] Of all the *Rhodiola* species, *R. rosea* has been the predominant subject of phytochemical, animal, and human studies.[2,18,23,24] Table 2 compares the research record of *R. rosea* with all other species of the genus *Rhodiola*. Approximately 51 percent of all animal studies and 94 percent of all human studies conducted on plants in the genus *Rhodiola* are on the species *R. rosea*. Only *R. rosea* has passed extensive toxicological studies and has been certified safe for both animals and humans.[25]

Table 1. Distribution of plants in the genus Rhodiola

Asia: China (Gansu, Hebei, Jilin, Shanxi, Sichuan, Xinjiang); Kazakhstan and Uzbekistan; Mongolia; Russian Federation (Altai, Eastern Siberia, Kamchatka, Khabarovsk, Magadan)
Europe: Austria; Bulgaria; Czechoslovakia; Finland; France; Greenland; Iceland; Ireland; Italy; Norway; Poland; Romania; Russian Federation (European part); Spain; Sweden; United Kingdom; Yugoslavia
North America: Canada (British Columbia, Northwest Territory, Ykon Territory); United States (Alaska, California, Colorado, Isaho; Minnesota, Montana, Nevada, New Mexico, New York, Oregon, Tennessee, Utah, Virginia, Washington, Wyoming)

Phytochemistry of Rhodiola rosea

The investigation of the phytochemistry of *R. rosea* root has revealed the presence of six distinct groups of chemical compounds:

- Phenylpropanoids: rosavin, rosin, rosarin (specific to *R. rosea*;
- Phenylethanol derivatives: salidroside (rhodioloside), tyrosol;
- Flavanoids: rodiolin, rodionin, rodiosin, acetylrodalgin, tricin;
- Monoterpernes: rosiridol, rosaridin;
- Triterpenes: daucosterol, beta-sitosterol;
- Phenolic acids: chlorogenic and hydroxycinnamic, gallic acids.

The standardization of *R. rosea* root extracts has gone through two distinct phases. Initially, in the 1970s, the compound responsible for its unique pharmacological properties was believed to be salidroside (rhodioloside).[2,23,24,26,27] Therefore, the first generation of *R. rosea* tincture/extracts approved by the Russian Pharmacopoeia Committee was standardized to a minimum of 0.8 percent salidroside content.[25]

In the late 1980s, demand for *R. rosea*-based phytomedicines dramatically increased. The wild-crafted raw material was over-harvested, resulting in a steady decline in the quality and effectiveness of "*Rhodiola*" preparations. Scientific investigation revealed that other species of genus *Rhodiola* (which also contained salidroside) were being substituted for *R. rosea*. While some of these mixed batches were highly variable in quality, others had no

pharmacological effect. Logically, the suspicion arose that the salidroside standard was inadequate. Based on comparative analysis, the obvious hypothesis was that the original high potency product contained other active compounds specific to *R. rosea* that had not yet been identified.

Specific compounds set Rhodiola rosea apart from other Rhodiola species

After more than a decade of research, Kurkin and colleagues presented evidence in 1986 that the chemical composition of *R. rosea* root is, in fact, different from the other species of genus *Rhodiola*.[23] Using newly developed methods of analysis, Dubichev and colleagues demonstrated that *R. rosea* root contains three cinnamyl alcohol-vicianosides — rosavin, rosin, and rosarin — that are specific to this species.[28,29] The term *rosavins* can be used to include rosavin, rosin, and rosarin (see chemical figures).

It became evident that salidroside is present in all chemically analyzed plants in the genus *Rhodiola*, and in a wide variety of species outside the genus.[2,25-34] The term *salidroside* is derived from *Salix*, the genus name for the willows. Salidroside was first isolated in 1926 from *Salix triandra* L. (Salicaceae).[33] Since then it has been detected in *Vaccinium vitis-idaea* L. (Ericaceae) and in *Rhododendron*[35,36] (plants not belonging to the genus *Rhodiola*) in concentrations that can be higher than levels found in *Rhodiola* species, including *R. rosea*. Therefore, salidroside alone is not a useful marker compound for differentiating true *R. rosea* from other *Rhodiola* species; nor should it be used as the only marker compound for the standardization of *R. rosea* root extracts.

According to the revised 1989 Soviet Pharmacopeia,[37] 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 minimum 3 percent rosavins and 0.8-1 percent salidroside because the naturally occurring ratio of these compounds in *R. rosea* root is approximately 3:1.

Table 2. Comparison of human and animal studies of plants in the genus *Rhodiola* *

Species name	Animal Studies	Human Studies
R. rosea	32	17
R. alterna	0	0
R. brevipetiolata	0	0
R. coccinea	1	0
R. crenulata	4	1
R. ellipticum	0	0
R. fastigita	2	0
R. gelida	0	0
R. henryi	0	0
R. heterodonta	1	0
R. kirilowii	6	0
R. pinnatifida	1	0
R. quadrifidia	1	0
R. sachalinensis	6	0
R. sacra	5	0
R. wolongensis	1	0
R. yunnanensis	0	0

*NOTE: Numbers in this table indicate the number of animal and human studies on each plant species of the genus *Rhodiola*, according to a Copernic online database search, 2001. This article reviews many additional studies not listed in online databases.

Rhodiola rosea in Modern Medicine

Since 1969, *R. rosea* has been included in official Russian medicine. The Pharmacological and Pharmacopoeia Committee of the Soviet Ministry of Health recommended medicinal use and industrial production of liquid *R. rosea* extract. In 1975, the Soviet Ministry of Health approved and registered preparation No. 75/933/14 as a medicine and tonic, allowing large-scale production under the name Rhodiola Extract Liquid, an alcohol-based extract (40 percent ethyl alcohol). Medical and pharmacological texts describe its use as a stimulant for asthenia (fatigue), for somatic and infectious illnesses, in psychiatric and neurological conditions, and in healthy individuals to relieve fatigue and to increase attention span, memory, and work productivity. The common dose is 5-10 drops 2-3 times a day, 15-30 minutes before eating for a period of 10-20 days. In psychiatric disorders with fatigue, a starting dose of 10 drops 2-3 times a day is gradually increased up to 30-40 drops for 1-2 months.

In Sweden, *R. rosea* was recognized as an Herbal Medicinal Product in 1985 and has been described as an antifatigue agent in the *Textbook of Phytomedicine for Pharmacists*.[9] In the textbook of pharmacology for dispenser training in Sweden, *R. rosea* is mentioned as a plant with a stimulant action. Also, the *Pharmaceutical Book* (*Lakemedelsboken* 97/98) mentions *R. rosea* as one of the most commonly used psychostimulants in the group of officially registered herbal medicinal products.[11] In Denmark, *R. rosea* is registered as a medical product in the category of botanical drugs. Registered preparations are extensively used in

Sweden and other Scandinavian countries to increase mental work capacity during stress, as a psychostimulant, and as a general strengthener.

Pharmacological and Clinical Studies

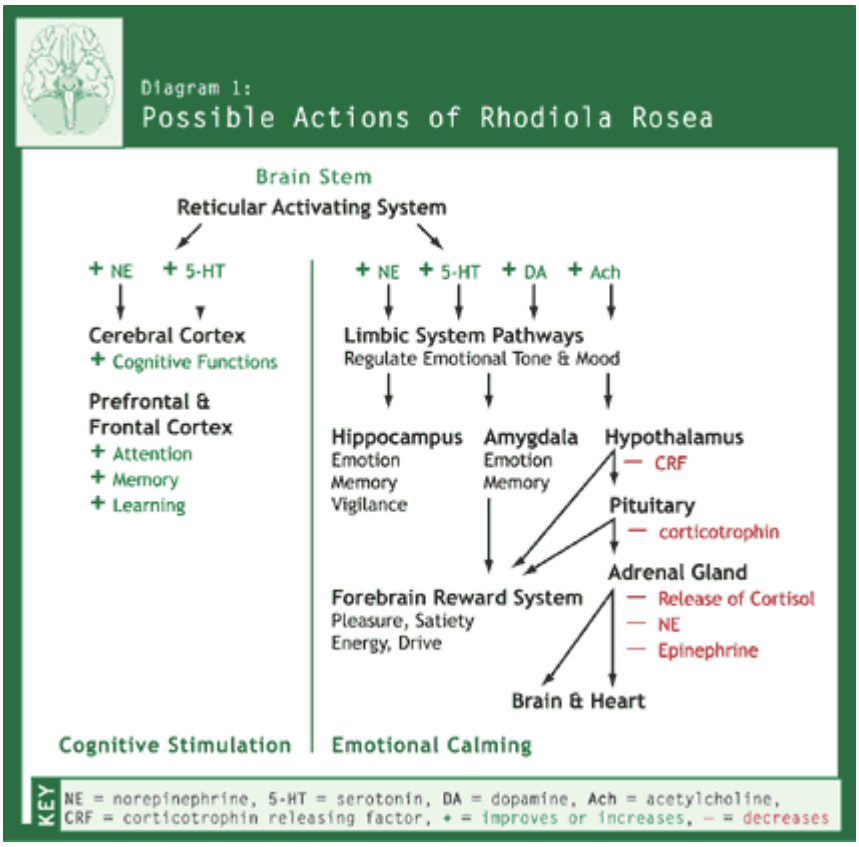
The traditional use of *R. rosea* as a tonic in Siberian and Russian medicine stimulated extensive research leading to identification of *R. rosea* as an adaptogen — a substance that nonspecifically increases the resistance of an organism and does not disturb normal biological parameters. Studies in cell cultures, animals, and humans have revealed antifatigue, anti-stress, antihypoxic (protection against damaging effects of oxygen deprivation), anticancer, antioxidant, immune enhancing and sexual stimulating effects.[2,18,24,38-40] Since the Russian and Bulgarian literature is so extensive, this discussion will highlight seminal studies and major reviews. The authors were fortunate to gain access to original reviews, articles, and doctoral theses. This overview relies heavily on monographs and peer-reviewed publications. The research data contained in these documents are helpful for understanding recent human studies in normal and pathological conditions.

Effects upon the Central Nervous System

The systematic study of the pharmacological effects of *R. rosea*, begun in 1965, found that small and medium doses had a simulating effect, such as lengthening the time mice swim and remain on vertical perches to the limit of their abilities. In contrast, larger doses were found to have more sedative effects. Small doses increased the bioelectrical activity of the brain, presumably by direct effects on the brainstem ascending and descending reticular formation.[23-26,38,39,41] Further studies showed that medium range doses, unlike tranquilizers, enhanced the development of conditioned avoidance reflexes in rats and facilitated learning based on emotionally positive reinforcement.[18,42-46] Overall, in small and medium doses, *R. rosea* stimulated norepinephrine (NE), dopamine (DA), serotonin (5-HT), and nicotinic cholinergic effects in the central nervous system (CNS). It also 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.[2,23,42,46-49]

In comparing studies of *R. rosea*, Asian ginseng (*Panax ginseng* C.A. Mey., Araliaceae), meclofenoxate (centrophenoxine), piracetam, citicholine, and other nootropics (substances that enhance cognition, protect the brain, and have low toxicity and few side effects), Petkov and colleagues noted that all of these agents enhance learning and memory in animal models and increase 5-HT levels in the frontal cerebral cortex.[46-50] Diagram 1 illustrates the possible effects of *R. rosea* on neurotransmitters in multiple neuronal pathways.[51] Starting in the brain stem, *R. rosea* promotes release of NE, 5-HT, and DA in ascending pathways that activate the cerebral cortex and the limbic system.[2,49,50] 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 are enhanced. Other neuronal systems also contribute to the many aspects of memory: encoding, sorting, storage, and retrieval. For example, the cholinergic system uses the neurotransmitter acetylcholine (Ach) and contributes to memory function via pathways ascending from the memory storage systems of 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* reverses this blockade.[49,50] The deterioration of these systems with age results in age-associated memory loss.[52] *R. rosea* may prevent or ameliorate some age-related dysfunction in these neuronal systems.



As an antioxidant,[53-55] *R. rosea* may help protect the nervous system from oxidative damage by free radicals. Stress interferes with memory functions and, over time, causes deterioration in memory systems. In addition to enhancing cognitive functions, learning, and memory by stimulating NE, DA, 5-HT, and Ach neuronal systems, *R. rosea* may exert positive effects on memory and cognition by improving resistance to physical and emotional stress. Thus, the dual action of cognitive stimulation and emotional calming creates benefits for both immediate cognitive and memory performance and for the long-term preservation of brain functions.

The psychostimulant effects of *R. rosea* were studied in 53 healthy subjects and 412 patients with neuroses and asthenic syndromes (of both functional and organic origin).[56-58] Symptoms of asthenia (fatigue, decline in work capacity, trouble falling asleep, poor appetite, irritability, and headaches) responded favorably to *R. rosea* 50 mg three times a day. Treatment durations ranged from 10 days to 4 months. The asthenic states included both psychiatric and physical causes, for example, following influenza or other illness. In an open study of 128 patients aged 17-55 years, *R. rosea* alleviated fatigue, irritability, distractibility, headache, weakness and other vegetative symptoms in 64 percent of cases.[57] Improvement was assessed by psychological testing and work productivity.

In 1869 Beard coined the term "neurasthenia" to include various forms of nervous asthenia. Controversy over this term has centered on the overlap of symptomatology and co-morbidity

with other conditions (e.g., depression, neuroses, somatoform disorders, and chronic fatigue syndrome). Although this diagnosis has fallen out of favor in the United States and no longer appears in *The Diagnostic and Statistical Manual of the American Psychiatric Association* (DSM-IV),[59] it is still widely used throughout the world.[60-63] Neurasthenia is defined by the World Health Organization in the *International Classification of Diseases* (ICD-10)[64] as:

- either persistent and distressing feelings of exhaustion after minor mental effort, or persistent and distressing feelings of fatigue after minor physical effort;
- accompanied by one or more of the following symptoms: muscular aches or pains; dizziness; tension headaches; sleep disturbance; inability to relax; and irritability;
- inability to recover through rest, relaxation, or enjoyment;
- does not occur in the presence of organic mental disorders, affective disorders or panic, or generalized anxiety disorder.

In an open study 27 healthy students, physicians, and scientists aged 19-46 years were given 10 drops of *R. rosea* tincture (equivalent to 100-150 mg *R. rosea* extract) once or twice a day for 2-3 weeks, beginning several days before intense intellectual work, such as final exams.[58] The extract improved the amount and quality of work and in all cases prevented asthenic decompensation (loss of work capacity due to fatigue). A series of studies using a proofreading test showed that a one-time dose of *R. rosea* did not significantly increase the number of symbols corrected, but very significantly decreased the percent of errors made, particularly over an 8-hour period.[65,66] Positive results found in the studies of proofreading tests were based on 300 mg/day or more. In medical treatments, the usual doses are 200-600 mg/day. *R. rosea* increased intellectual capacity (particularly by improving perception and processing of information) to a greater degree than an extract of eleuthero, formerly called Siberian ginseng (*Eleutherococcus senticosus* Rupr. et Max., Araliaceae).[18]

The decrease in physical and mental performance of physicians on prolonged night call is well known. Low dose (170 mg/day) *R. rosea* extract was given to 56 young, healthy physicians on night call.[18] 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 three periods of two weeks 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 first two-week period. However, at 6 weeks the effect appeared to be lost. No side effects were reported. These results suggest that *R. rosea* extract can reduce fatigue under certain stressful conditions for some period of time. Possible reasons for the loss of efficacy over 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.

Spasov and colleagues compared 100 mg/day *R. rosea* extract (SHR-5, Swedish Herbal Institute, Goteborg, Sweden; standardized to 3 percent rosavin and 0.8 percent salidroside) with placebo in a double-blind 20-day study of 60 Indian medical students studying in Russia during their final exam period.[38] Despite the low dosage, investigators found significant improvements in general well-being, physical fitness, mental fatigue, final exam grades, and coordination, but not in some aspects of cognitive functioning in students taking *R. rosea* extract compared to placebo.

In a double-blind placebo-controlled study of 60 foreign students at a Russian high school, administration of a *R. rosea* extract (660 mg/day of a preparation named Rodaxon) resulted in an increase in physical (velergometric) work capacity, coordination, kinesthetic sensitivity, and general well-being along with a decrease in psychic fatigue and situational anxiety.[39] Unfortunately, this study provides no information on the amount of *R. rosea* in the Rodaxon preparation.

R. rosea was beneficial in posttraumatic and vascular lesions of the brain. It was especially effective in combination with piracetam for patients with marked cognitive dysfunction.[56] However, it did not reduce manic symptoms and could worsen paranoid states. In one study of more clearly depressed patients, *R. rosea* in combination with tricyclic antidepressants (TCAs) produced significant improvement in the majority of cases and decreased side effects of the TCAs.[67] Ultimately, some of these patients were able to respond to *R. rosea* alone.

Antipsychotic medications used in large doses over many years to treat schizophrenic patients sometimes affect the dopaminergic nerves in the basal ganglia, the same nerves that are damaged in patients with Parkinson's Disease. When these nerves are compromised, patients develop a constellation of "Parkinsonian" symptoms, including stiffness, tremors, bradykinesia (slowed movements), and others. Anticholinergic medications have been used to relieve these symptoms when they are caused by antipsychotic medication; however, they sometimes fail to help. In schizophrenic patients whose anticholinergic medications had failed to relieve Parkinsonian symptoms, *R. rosea* was found to be of benefit.[56,68]

R. rosea may affect emotional tone by influencing neurotransmitter monoamine levels (NE, DA, 5-HT) in nerve tracts involved in the regulation of mood, anxiety, and emotion in the amygdala, hippocampus, hypothalamus, and midbrain. 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 underlie this complex spectrum of psychotropic activity: stimulating, tranquilizing, anti-stress, and antidepressant.

The authors have found that *R. rosea* can help patients with depressive syndromes, mental and physical fatigue (secondary to psychiatric and medical conditions), memory loss and cognitive dysfunction from a variety of causes, sexual dysfunction, and menopausal-related disorders. Dr. Brown and Dr. Gerbarg have successfully treated more than 150 individuals with *R. rosea* extract (3 percent rosavin and 1 percent salidroside) and have supervised the treatment of more than 100 additional cases (See Case Studies).

Effects on Physical Work Capacity

A number of studies have shown that *R. rosea* increased physical work capacity and dramatically shortened the recovery time between bouts of high-intensity exercise. These studies included normal individuals exposed to maximal work on a bicycle ergometer and Olympic-level cross country skiers and biathletes.[69] In one study, 52 men (18-24 years of age) were given one dose of either 15 drops of *R. rosea* extract, 2 ml eleuthero, or 1 ml of a 1 percent solution piridrol (a stimulating psychotropic similar to methylphenidate). Fifteen drops of *R. rosea* extract is approximately equivalent to 150 mg of dry encapsulated root extract standardized to 3 percent rosavin and 1 percent salidroside. After 30 minutes, they pedaled an electric bicycle ergometer to produce a precise amount of work-induced baseline fatigue. After a 5-minute rest, they performed further work to determine the maximal duration

of work they could accomplish at a specific intensity. During the second period of work, *R. rosea* drops, eleuthero extract, and piridrol increased work capacity by 9 percent, 6 percent, and 6 percent respectively ($p<0.04$) compared to placebo controls. Recovery was defined by the time of normalization of heart rate and arterial pressure. During the recovery period, at 10 minutes, the pulse slowed by a factor of 2.5 (67 beats per minute) in the *R. rosea* group versus 1.9 (87 beats per minute) in the control group. During the 3-day total recovery period, subjects given piridrol complained of insomnia, excitability, and irritability; whereas those given *R. rosea* had no adverse side effects and no complaints.

Endurance is the capacity to maintain work despite fatigue. Forty-two master level competitive skiers (20-25 years of age) took either *R. rosea* extract or placebo 30-60 minutes before training races (30 km) and a biathlon (20 km race on skis carrying a rifle and shooting targets at stops). Athletes given *R. rosea* had statistically significant increased shooting accuracy, less arm tremor and better coordination. Thirty minutes after work performance, the heart rate in the *R. rosea* group was 104-106 percent of baseline, versus 128.7 percent in the placebo group ($p<0.02$). *R. rosea* improved recovery time, strength, endurance, cardiovascular measures, and coordination.[69]

Adaptogens differ from other stimulants during forced, exhaustive muscular work. With classical stimulants the initial increase in work-capacity is followed by a period of substantially decreased (markedly below average) work-capacity. Repeated use of CNS 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.[70]

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 in mice made to swim to their limit.[71] It may also enhance the ammonia reassimilation and energy metabolism of the cell by increasing ATP, ribonucleic acid (RNA), protein, and amino acid synthesis.[72] In animal studies, *R. rosea* increased metabolism of fats twice as much as eleuthero[73] and improved energy metabolism in the brain during intensive muscular workloads.[74]

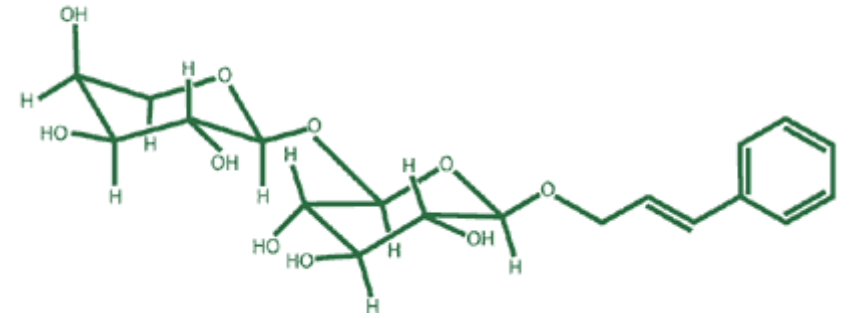
Adaptogenic, Anti-Stress, and Neuroendocrine Effects

In their classic 1968 paper, Soviet pharmacologists Brekhman and Dardymov surveyed the literature on 189 medicinal plants and identified five (including *R. rosea*) that met the three defining criteria for an adaptogen:[75]

- An adaptogen should be innocuous and cause minimal disturbance of the normal physiological functions of an organism;
- The action of an adaptogen should be nonspecific (i.e., it should increase resistance to adverse influences of a wide range of harmful factors of physical, chemical, and biological nature);
- An adaptogen may possess normalizing action irrespective of the direction of the preceding pathological changes (i.e., if a body parameter is high, the adaptogen brings

it down towards normal; if a parameter is low, the adaptogen brings it up towards normal).

Figure 1: Rosavin

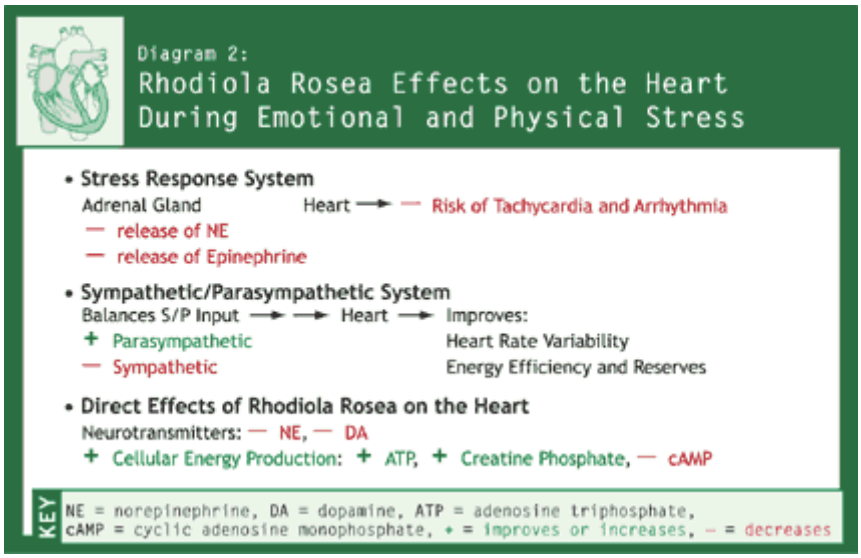


The forced swimming test, used by Russian scientists to measure nonspecific resistance to stress, was later named after Porsolt who assigned specific parameters such as water temperature and the dimensions of the glass cylinder in which a mouse or rat was forced to swim to exhaustion (about 15 minutes). After an initial period of vigorous activity, the rodent adopts a characteristic immobile posture, making only the minimal movements necessary to stay afloat.[76] The validity of the Porsolt swim test and its relationship to depression have been discussed extensively[77,78] and it subsequently became a screening test for antidepressant agents by pharmaceutical companies. Although different laboratories have made minor technical modifications, the fundamentals of the test remain the same. Adaptogens and antidepressants increase the amount of time the animal is able to keep swimming actively.[75] Panossian and colleagues propose to update the definition of adaptogen by highlighting more specific biochemical actions as metabolic regulators.[70] The wide range of medical benefits and physiological actions may be based on the effects of adaptogens on regulatory systems found in many organs and tissues (e.g., immune, hormonal, CNS, cardiovascular, muscular, etc.). They hypothesize that adaptogens reduce damage from stressors by altering the reactivity of the organism's defense system, including the hypothalamic pituitary axis (HPA) and the efferent sympatho-adrenal system (SAS).[70]

A recent study showed that *R. rosea* and eleuthero protected the embryos of freshwater snails (*Lymnaea stagnalis*) from a variety of environmental stressors.[79] Enhancement in resistance was studied by applying phyto-adaptogen extracts for a period of 20 hours to 3-day old *L. stagnalis* larvae. Subsequently the larvae were exposed to the following highly toxic environmental stressors: a physical stress (heat shock: 43 degrees C for 4 minutes); an oxidative stress (superoxide radicals induced by menadione 600 microM for 2 hours); and heavy metal-induced stress (copper 50 microM for 1 hour or cadmium 20 microM for 1 hour). Both eleuthero and *R. rosea* strongly protected snail embryos from lethal heat shock, from the adverse effects of menadione-induced superoxide radicals, and from toxic exposure to heavy metals (copper and cadmium). Although the degree to which resistance was enhanced depended on the type of stressor applied, these results confirm the definition of phyto-adaptogens as being universal enhancers of non-specific resistance against different kinds of stress conditions. The mechanisms of nonspecific resistance are not entirely clear, but probably involve improvements in cellular energy metabolism, based in part on ATP (as discussed above).

In higher animals and humans, nonspecific resistance may also be enhanced by improvements in the neurological mechanisms of 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 hypothalamic pituitary adrenal axis and participation of the gonads and thymus were necessary for this anti-stress effect.[2] Furthermore, *R. rosea* reduces the activation of several components of the stress response system. For example, it modestly increased serum beta-endorphins that protected rats against subsequent stress-induced excess endorphin elevation.[80] In addition, *R. rosea* moderates the release of opioid peptides that occurs as part of the pituitary adrenal axis response to stress. This reduced release protects against sudden excess opioid and catecholamine (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 (see Diagram 2). *R. rosea* extracts also protect the brain and heart by reducing the secretion of corticotrophin releasing factor (CRF) under stress.[80,81]



Endocrine and Reproductive Effects

Neuroendocrine animal studies showed that *R. rosea*, like other adaptogens, enhanced thyroid function without causing hyperthyroidism.[81] In addition, the thymus gland functioned better and was protected from the involution that occurs with aging. The adrenal glands 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 effects 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 weeks prolonged menstruation from 1.3 days (control) to 2.8 days (rhodosin treated), reduced the resting period from 3.8 days (control) to 2.2 days (rhodosin treated), and increased the relative number of estrus days from 29 percent to 56 percent. 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 all 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 weeks 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 upon a specific hormonal milieu.[82,83]

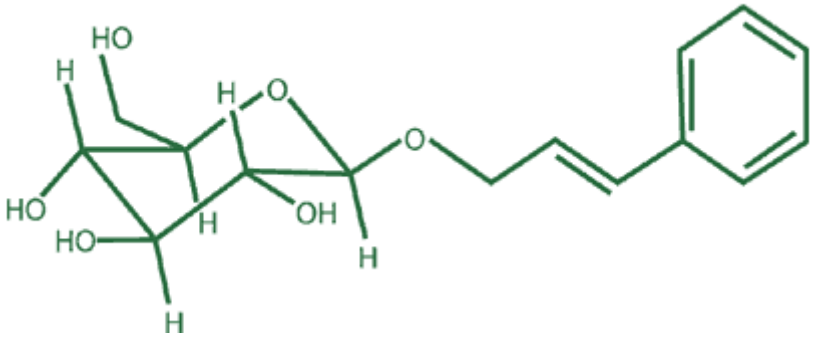
These pre-clinical investigations led to a study of *R. rosea* extract in women suffering from amenorrhea (loss of menstrual cycles). Forty women with amenorrhea were given *R. rosea* (either 100 mg *R. rosea* extract orally twice a day for 2 weeks, or 1 ml rhodosin intramuscularly for 10 days). In some subjects the treatment cycle was repeated 2-4 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.[82,83] One of the authors (Dr. Brown) has treated in his practice several women who had failed to conceive with standard fertility drugs, and who become pregnant within several months of beginning *R. rosea* extract. These preliminary clinical observations warrant controlled follow-up clinical trials. Using the *in vitro* estrogen receptor competition assay, Patricia Eagon, Ph.D. (personal communication, December 2001) recently found that *R. rosea* extract showed strong estrogen binding properties that require further characterization.

In an open study, 26 out of 35 men with erectile dysfunction and/or premature ejaculation (of 1-20 years duration) responded to *R. rosea* (150-200 mg/day for 3 months) with substantially improved sexual function, normalization of prostatic fluid, and an increase in 17-ketosteroids in urine.[56,69]

Cardioprotective Effects

Cardioprotective effects of *R. rosea* include: prevention of stress-induced cardiac damage,[80,81,84] decreased myocardial catecholamines and cyclic adenosine monophosphate (cAMP) levels; and reduced adrenal catecholamine release[80,81] (see Figure 2). Furthermore, *R. rosea* activation of mu-opiate receptors in heart muscle prevented reperfusion arrhythmias in animal hearts. 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.[84]

Figure 2: Rosin



In a series of joint Swedish and Russian double-blind, randomized placebo-controlled studies,[85] 10 healthy but sedentary men (ages 20-31 years) were evaluated. Twenty percent of the subjects had average physical work capacity as measured by Power Work Capacity (PWC-170) and 80 percent had below-average PWC-170, indicating a low level of physical training (PWC-170 is a calculation based on the amount of work performed by a man if his heart rate reaches 170 beats per minute, bpm). A sequence of complex 1- to 7-day trials compared the effects of an adaptogen formula, a mixture of mono- and polyphenolic adaptogens (MMPA). Each tablet contained the following ingredients: 3 mg rhodioloside from *R. rosea* root extract, 50 mg; 3 mg total sum of isofraxidine-, syringine-, and syringaresinoie-glycosides from eleuthero root extract, 100 mg; and 4 mg schizandrine and gamma-schizandrine from schisandra (*Schisandra chinensis* (Turcz.) Baill., Lamiaceae) fruit extract, 150 mg.

During the 7-day adaptogen trial, subjects were given 3 capsules (containing a total of 150 mg *R. rosea*) twice a day on days 1-3; 4 capsules (200 mg *R. rosea*) twice a day on days 4-6, and 4 capsules once on day 7. The mean increase in physical work capacity was 28 percent with dosed physical loads in subjects treated with the adaptogen formula. Thus, sedentary subjects given the adaptogen were able to perform in the lower level of trained athletes without any exercise training. Their heart rate variability and inotropic (strength of heart muscle contractility) functions improved.

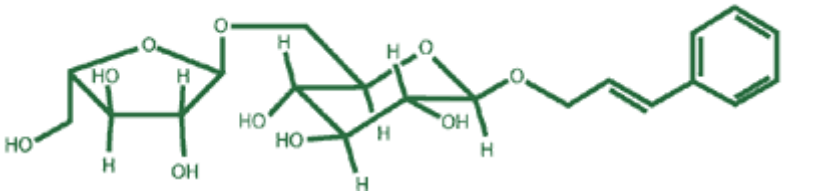
Both the sympathetic and parasympathetic inputs to the heart were enhanced such that the heart showed increased reserves under stress of greater intensity. The autonomic nervous system controls automatic or involuntary functions of the body. It has two components: the sympathetic and the parasympathetic nerves (see Diagram 2). The sympathetic nervous system is the "fight-or-flight" system that helps the organism respond to stress (e.g., by increasing heart rate, respiratory rate, and muscle tone). The parasympathetic nervous system conserves and restores energy (e.g., 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 one single herbal component. However, the results of this study are consistent with results of other research conducted solely on *R. rosea* monopreparations.

Antioxidant and Anti-carcinogenic Effects

R. rosea is rich in phenolic compounds, known to have strong antioxidant properties.[53,86] Animal studies have shown that *R. rosea* decreases toxicity from cyclophosphamide, rubomycin, and adriamycin (anti-cancer drugs), while it enhances their anticarcinogenic effects.[87-89] Udintsev and Schakhov studied the effect of *R. rosea* root extract (RRRE), a tincture manufactured according to the Russian Pharmacopoeia standards (minimum 0.8 percent salidroside and 3 percent rosavin), on tumor cells (transplanted into mice) and normal bone marrow cells in two mouse cancer models.[90] One group of mice with Ehrlich ascites tumor (EAT) and another group with Lewis lung carcinoma (3LL) were first treated with 100 mg/kg cyclophosphamide (a chemotherapy agent) that suppressed tumor growth to 31-39 percent and limited 3LL metastases to 18 percent, while also reducing the number of normal bone marrow cells, leucocytes, and myelokariocytes, to 40-50 percent and 20-25 percent of normal, respectively. In comparison, RRRE, 0.5 mg/kg/day given orally 2-8 days after tumors

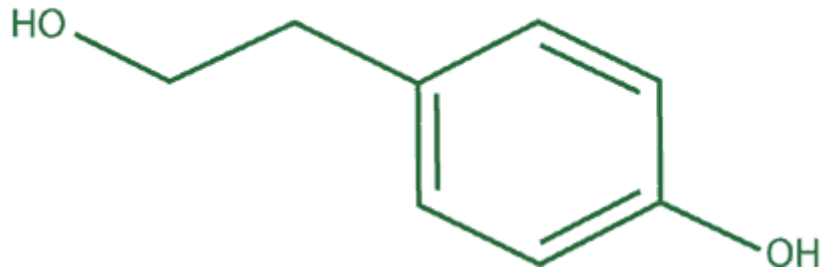
had been transplanted, suppressed growth of both tumors by 19-27 percent and 3LL metastases 16 percent. However, in contrast to cyclophosphamide, RRRE caused no reduction in normal bone marrow cells. In animals given both RRRE and cyclophosphamide, the RRRE increased the antimetastatic effect of cyclophosphamide by 36 percent ($p<0.05$). RRRE also increased the number of leukocytes by 30 percent and myelokariocytes by 16-18 percent.

Figure 3: Rosarin



In another mouse tumor model, Udintsev and colleagues showed that RRRE (minimum 0.8 percent salidroside and 3 percent rosavin) increased the antitumor effect of the drug adriamycin while substantially reducing its liver toxicity.[89] 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 while alleviating dangerous side effects.

Figure 4: Tyrosol



Substances that reduce the incidence of chromosomal aberrations are termed antimutagenic. Salikhova and colleagues found that in mice injected with cyclophosphamide, RRRE (minimum 0.8 percent salidroside and 3 percent rosavin) had antimutagenic effects.[91] Compared to placebo controls, RRRE reduced the development of chromosomal aberrations by 50 percent and reduced the incidence of cells with micronuclei by more than 50 percent. RRRE also increased indices of DNA repair in bone marrow cells after exposure to the mutagen N-nitroso-N-methylurea (NMU).[91]

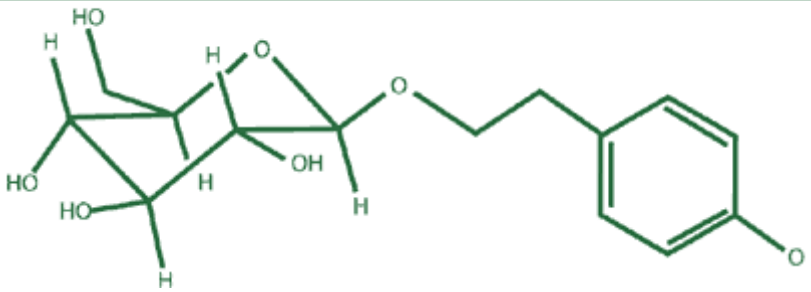
In a small pilot study of 12 patients with superficial bladder carcinoma (TIG1-2), treatment with RRRE (minimum 0.8 percent salidroside and 3 percent rosavin) improved parameters of leukocyte integrines and T-cell immunity.[92] The average frequency of relapse was reduced, but did not reach statistical significance. Larger placebo-controlled studies of *R. rosea* extracts to augment tumor inhibition and reduce toxic effects of chemotherapy agents are needed.

Toxicity, Side Effects, and Contraindications

R. rosea has a very low level of toxicity. In rat toxicity studies, the LD_{50} (lethal dose at which 50 percent of animals die) was calculated to be 28.6 ml/kg, approximately 3,360 mg/kg.[25] The equivalent dosage in a 70 kg man would be about 235 gm or 235,000 mg. Since the usual clinical doses are 200-600 mg/day, there is a huge margin of safety.[87]

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 first few weeks. It is contraindicated 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. Until this has been further studied, the authors advise caution in patients with bipolar spectrum disorders. The herb does not appear to interact with other medications, though it may have additive effects with other stimulants. It is best absorbed when taken on an empty stomach 30 minutes before breakfast and lunch. As with any herbal preparation, patients should inform their primary healthcare practitioner when taking *R. rosea*.

Figure 5: Salidroside



Rhodiola in the Future

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 post traumatic stress disorder), and enhancement of chemotherapy/radiation with amelioration of toxicity.

In the course of 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 years ago to its use by 20th century cosmonauts. It is time for modern research, using controlled clinical trials, to develop the potential medical applications of this unique phyto-adaptogen.

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Acknowledgement: The authors are grateful to Dr. Bertalan Galambosi from Agrifood Research Finland, Ecological Production, of Mikkeli, Finland, for providing the photographs of Rhodiola rosea.

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