

## Sharper Mind™ Product Science – *Rhodiola rosea* Monograph

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### **Rhodiola rosea: A Phytomedicinal Overview**

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*Rhodiola rosea* L., also known as "golden root" or "roseroot" belongs to the plant family Crassulaceae.<sup>1</sup> *R. rosea* grows primarily in dry sandy ground at high altitudes in the arctic areas of Europe and Asia.<sup>2</sup> 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*.<sup>3</sup> Linnaeus renamed it *Rhodiola rosea*, referring to the rose-like attar (fragrance) of the fresh cut rootstock.<sup>4</sup>

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.<sup>2,4-12</sup> 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.

### **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: rodilin, rodionin, rodiosin, acetylrodalgin, tricin;
- Monoterpenes: 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).<sup>2,23,24,26,27</sup> 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.<sup>25</sup>

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*.<sup>23</sup> 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.<sup>28,29</sup> 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.<sup>2,25-34</sup> The term *salidroside* is derived from *Salix*, the genus name for the willows. Salidroside was first isolated in 1926 from *Salix triandra* L. (Salicaceae).<sup>33</sup> Since then it has been detected in *Vaccinium vitis-idaea* L. (Ericaceae) and in *Rhododendron*<sup>35,36</sup> (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,<sup>37</sup> 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.

### **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*.<sup>9</sup> 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.<sup>11</sup> 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.<sup>2,18,24,38-40</sup> 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 stimulating 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.<sup>23-26,38,39,41</sup> 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.<sup>18,42-46</sup> 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.<sup>2,23,42,46-49</sup>

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.<sup>46-50</sup> Diagram 1 illustrates the possible effects of *R. rosea* on neurotransmitters in multiple neuronal pathways.<sup>51</sup> 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.<sup>2,49,50</sup> 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.<sup>49,50</sup> The deterioration of these systems with age results in age-associated memory loss.<sup>52</sup> *R. rosea* may prevent or ameliorate some age-related dysfunction in these neuronal systems.

As an antioxidant,<sup>53-55</sup> *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).<sup>56-58</sup> 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.<sup>57</sup> Improvement was assessed by psychological testing and work productivity.

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.<sup>58</sup> 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 proof-reading 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.<sup>65,66</sup> Positive results found in the studies of proof-reading 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).<sup>18</sup>

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.<sup>18</sup> 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.<sup>38</sup> 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.<sup>39</sup> 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.<sup>56</sup> 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.<sup>67</sup> 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.<sup>56,68</sup>

*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

### **Toxicity, Side Effects, and Contraindications**

*R. rosea* has a very low level of toxicity. In rat toxicity studies, the LD<sub>50</sub> (lethal dose at which 50 percent of animals die) was calculated to be 28.6 ml/kg, approximately 3,360 mg/kg.<sup>25</sup> 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.<sup>87</sup>

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*.

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