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**File: ■ Rhodiola (*Rhodiola rosea*, Crassulaceae)
■ Depression**

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RE: Review of Rhodiola in the Treatment of Depression

Amsterdam JD, Panossian AG. *Rhodiola rosea* L. as a putative botanical antidepressant. *Phytomedicine*. June 15, 2016;23(7):770-783.

In addition to enhancing energy and performance, the botanical adaptogen rhodiola (*Rhodiola rosea*, Crassulaceae) root and rhizome is used to counter the effects of stress and fatigue. Stress and fatigue are common symptoms in patients with depression. In this article, the authors review the scientific evidence supporting the potential efficacy of rhodiola in the treatment of depression.

STN Easy service was used to search all comprehensive databases including BIOSIS, CAPLUS, EMBASE, NAPRALERT, PubMed, TOXCENTER, etc. The Russian State Library (Moscow, Russia) and the library of the Swedish Herbal Institute (Vallberga, Halland, Sweden) also were searched. The latter facility contains a complete collection of full-text Russian articles on this topic and their English translations dating back to 1943. Search terms were not specified.

Experimental evidence

Early studies conducted in the former Soviet Union between 1965 and 1986 found that rhodiola extract increased bioelectrical activity in the brain, enhanced conditioned avoidance behavior and facilitated learning in rats, and a single dose of extract improved learning and attention in rats 24 hours and ten days after administration.

Studies conducted between 2002 and 2015 have reported more detailed results. Administration of rhodiola extract for three weeks ameliorated behavioral and metabolic responses to chronic stress in rats, comparable to the antidepressant fluoxetine. Rhodiola root and rhizome extract had antidepressant activity in the despair forced swimming test, comparable to that of the antidepressants imipramine and amitriptyline. This effect was evident after a single oral dose. In the same animal model, the effects of rhodiola extract and rhodiola constituents were compared to imipramine and St. John's wort (*Hypericum perforatum*, Hypericaceae) flowering tops. The rhodiola extract exerted greater antidepressant effects than comparable doses of imipramine and St. John's wort; the constituents rhodioloside (salidroside) and tyrosol were active, while rosavin, rosarin, rosin, cinnamic alcohol, cinnamaldehyde, and cinnamic acid were inactive. However, in

another study, a fixed combination of rhodioloside, rosavin, rosarin, and rosin was more effective than any of the individual compounds alone, suggesting a synergistic effect.

Several studies using animal models of depression have provided evidence that rhodiola extract modulates neurotransmitter levels in the hippocampus, brainstem, cerebral cortex, and hypothalamus. It has also been reported to promote proliferation and differentiation of neural stem cells, and to increase the permeability of the blood-brain barrier to precursors of dopamine and serotonin. In rabbits exposed to stress, seven days of treatment with rhodiola extract and rhodioloside significantly inhibited the stress response mediator phosphorylated kinase (JNK). In a rat model of depression, two weeks of treatment with rhodioloside decreased tumor necrosis factor- α and interleukin- 1β levels, increased the expression of glucocorticoid receptor and brain-derived neurotrophic factor, and decreased levels of corticotropin-releasing hormone.

Mechanisms of action

The mechanisms of action of rhodiola extract and its constituents have been studied in cell cultures, nematodes, rodents, and humans. These studies have provided evidence that the antidepressant effect of rhodiola may be associated with the following mechanisms: modulation of stress response mediators, modulation of the hypothalamic-pituitary-adrenal axis homeostasis, modulation of G-protein coupled receptor signaling pathways, and stimulation of expression and release of neuropeptide Y (NPY). In addition, rhodiola extract has been shown to modulate the expression of over 50 genes which are thought to be involved in the pathogenesis of depression. Although the constituent rosiridin has been found to be an active inhibitor of monoamine oxidase A, the authors point out that the amount of this compound found in rhodiola extract is so minute that it precludes monoamine oxidase inhibition as the antidepressant mechanism.

Early clinical studies (1966-1986)

The authors point out that the early clinical trials conducted in the former Soviet Union (n=7) are of poor quality and difficult to interpret because of the following: studies were not randomized, most studies were not controlled or blinded, standardized psychological measures were not used, and some of the trials enrolled both healthy and depressed subjects. Moreover, the diagnostic criteria for depression used were different from those employed in other countries and as a result, patients with varying psychological conditions were enrolled (depression, asthenic-depressive syndrome, neurosis, and anxiety).

The results of these early studies may be briefly summarized as follows: treatment with rhodiola extract for two to three weeks had antidepressant effects in healthy subjects and in subjects with pronounced fatigue; patients with insomnia, irritability, and somatic complaints treated for ten days had improved motor and cognitive function, as well as lower irritability and lower anxiety levels; and three studies reported that rhodiola as an adjunct to psychotropic drugs not only had an additive effect but also reduced the adverse effects of the drugs.

Recent clinical trials (2007-2015)

In a 2008 open-label study of ten patients with generalized anxiety disorder, 340 mg of RhodaX™ (Bodyonics Ltd.; Hicksville, New York) daily for ten weeks resulted in a significant lessening of Hamilton Anxiety Rating Scale (HAM-A) scores (P=0.01) and Hamilton Depression Rating Scale (HAM-D) scores (P=0.001).

A 2007 randomized, double-blind, placebo-controlled trial investigating the effect of the rhodiola extract SHR-5 (Swedish Herbal Institute) in 89 patients with mild to moderate depression compared six weeks of treatment with daily dosages of 340 mg and 680 mg to placebo. HAM-D scores significantly improved in both dosage groups ($P < 0.0001$ for both) compared to baseline, while no significant change was observed in the placebo group; compared to placebo, the improvement in both dosage groups was significant ($P < 0.001$). However, the results of this trial have been questioned. First, there is invariably a significant placebo response in all placebo-controlled antidepressant trials and this trial reported no significant change from baseline in the mean score for the placebo group. Second, the "magnitude [of the treatment effect] is unlikely in an under-powered pilot trial of this design."

A 2015 randomized, double-blind, placebo-controlled study of patients with major depressive disorder compared 340 mg/day SHR-5 versus 50 mg/day sertraline versus placebo for 12 weeks. The SHR-5 capsules contained powdered extract standardized to a content of 3.07% rosavin and 1.95% rhodioloside (Investigational New Drug #105,063). The primary outcome was change in HAM-D score; secondary outcomes were changes in Clinical Global Impression (CGI) and Beck Depression Inventory (BDI) scores. There was no significant change in HAM-D, CGI, or BDI scores among treatment groups. However, there were clinically meaningful odds ratios of global improvement for rhodiola and sertraline versus placebo; compared to placebo, the odds of improvement were 1.4 for rhodiola and 1.9 for sertraline. More study-related adverse effects were reported in the sertraline group (63.2%) compared to the rhodiola (30.0%) and placebo (16.7%) groups.

The authors conclude that rhodiola "demonstrates multi-target effects on various levels of the regulation of cell response to stress, affecting various components of the neuroendocrine, neurotransmitter receptor and molecular networks associated with possible beneficial effects on mood." Rhodiola was well tolerated in the short-term clinical studies with a good safety profile. Despite the shortcomings of the human trials, the clinical evidence suggests that rhodiola "may represent a potential alternative treatment for individuals who are intolerant to conventional antidepressants or seek to avoid them." Larger, well-designed, and sufficiently powered clinical studies are needed to confirm the potential efficacy of rhodiola in the treatment of depression.

One of the authors (AG Panossian) is an employee of Swedish Herbal Institute.

—Amy C. Keller, PhD

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