

RhodioPrime 6X: Powered Adaptogen of the Vikings

What is Rhodiola?

The Rhodiola family of natural herbaceous plants includes 96 different species, which are commonly known as arctic root, rosenroot, orpin rose, or golden root.^[1-3] This herb is cultivated in the high-altitude, low-temperature areas of northern Europe and Asia and has been used for hundreds of years in China, Europe, North American, and by Vikings, who used it to increase endurance and physical strength.^[2] In traditional Chinese medicine (TCM), it is often used to enhance vitality and to provide support when feeling fatigued^[2]. In the 1960s, based on the results of numerous studies, Rhodiola was routinely incorporated in the Union of Soviet Socialist Republics as an adaptogen, as it was considered to exert energizing, balancing and stress resilience effects.^[4] The plant may be used by healthy individuals to provide support during periods of fatigue and stress. Additionally, it has been employed occupationally to provide support for adverse environmental challenges, including extreme conditions such as high noise levels and low temperature, and in clinical practice to provide nutritional support for heart health, cognitive function, metabolic function, liver health, well-being and more.^[5]

Since Rhodiola shows great potential with various capabilities, modern science is gaining more and more focus on it and especially on its extracts with a growing market for more effective formulations.

What is RhodioPrime 6X?

Although Rhodiola has been widely

investigated as an adaptogen, its mechanism(s) of action have not been elucidated well. For example, Rhodiola plants contain a complex array of chemical components (e.g., salidrosides, flavonoids, polysaccharides, terpenoids), which makes it difficult to thoroughly reveal the herb's capabilities; thus, only after separating and analyzing the Rhodiola root's constituents were scientists able to unveil the herb's capabilities. While there have been at least 140 compounds isolated from the roots of the Rhodiola, it is said that salidroside is the main bioactive compound.^[6]

RhodioPrime 6X is a Rhodiola extract with a salidroside content as high as 6%. As mentioned, salidroside is considered the main bioactive agent isolated from the roots of Rhodiola. Its chemical name is (4-hydroxy-phenethyl)- β -D-glucopyranoside and molecular weight is 300.3. Previous studies showed that salidroside has various biological effects, providing support for the cardiovascular system, nervous system, and liver,^[7, 8] and it may also help promote cognitive function.^[9] Its claimed benefits also include providing support for a healthy mood and feelings of well-being,^[10] healthy antioxidant status,^[11] healthy circulation and oxygenation ^[12, 13], anti-aging^[14] and vibrant energy levels.^[15]

What can RhodioPrime 6X do?

RhodioPrime 6X provides support for a range of overall health benefits including:

-Mental/Cognitive Support:

 Support for fatigue and stress management



•Support for mood and feelings of wellbeing

•Support for healthy BDNF levels

•Support for feelings of anxiousness and stress

•Support for healthy cognitive function -Exercise and Physical Performance Support:

•May help attenuate physical fatigue and promote performance

•May help improve exercise capacity

•May promote glucose uptake in skeletal muscle cells

-Antioxidant Support

• Provides support for healthy antioxidant status

-Hormonal Support

• Provides support for healthy estrogen metabolism

Highlights for Rhodiola Researches

1. Cognitive Support

The most important pathways by which Rhodiola (through salidroside) works as an adaptogenic is by promoting balance within the nervous system. Specifically, the herb has a profound relationship with the metabolism of neurotransmitters. There are five established biogenic amine neurotransmitters: the three catecholamines (e.g., dopamine, norepinephrine, and epinephrine), histamine, and serotonin, which regulate a variety of physiological functions, such as regulating cognitive abilities, mood, gut motility, the body's allergy and immune responses, and other biological processes.^[16, 17] The two major enzymes involved in the catabolism of catecholamines are monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT).^[18] Monoamine oxidases A and B (MAO-A and MAO-B), the two substrates of MAO, play central roles in neurotransmitter metabolism by metabolizing neurotransmitters in the brain. Research shows that the activity of these degrading enzymes may play a profound role in mood-related issues,^[8] such as feelings of worry and anxiousness^[9] and feelings of well-being,^[10] as well as other cognitive concerns.^[11] Hence, over the past several decades, there has been increased interest in natural products that may promote balanced MAO activity (and, therefore, healthy neurotransmitter activity) to provide cognitive and mental health support.

Apart from neurotransmitters, the body also utilizes neuropeptides as messengers to carry out biological actions. Neuropeptide Y (NPY) is one of the most influential of these neuropeptides in terms of orexigenic (i.e., appetite stimulating) signaling,^[19] controlling many of the cues and feelings associated with hunger. Moreover, as a neuropeptide widely distributed in the central and peripheral nervous system, NPY, which is referred to as a "stressresponsive" hormone, has also gained significant attention for its anti-stress and anxiolytic properties.^[20] Additionally, NPY is associated with cardiovascular regulation, cognition, and modulation of neuroendocrine systems as well.^[19]

As mentioned, studies have demonstrated that Rhodiola's biological properties are mainly attributed to salidroside, which has been shown to exert several adaptogenic functions.^[21] Importantly, recent studies have shown that salidroside may exert positive actions within the nervous system,^[22-24] in particular, providing support for healthy metabolism of β -amyloid



peptides *in vitro*^[25, 26] and *in vivo*.^[27] Additionally, numerous studies have shown that salidroside was able to influence the activity of MAOs ^[28, 29] and the expression of NPY ^[30, 31], and as a result, provide support for feelings of well-being, cognitive function, stress management and healthy appetite management.

MAO A and B inhibitory activities of Rhodiola rosea L. root extracts (at 100 µg/ml)
and the bio-guided isolated compounds (at 10^{-5} M).

Sample	Inhibition (%) ^b	
	MAO A	MAO B
DCM extract	50.5 ± 0.1	66.9 ± 0.3
MeOH extract	92.5 ± 0.1	81.8 ± 0.3
Water extract	84.3 ± 0.8	88.9 ± 0.3
Fraction G-2	96.8 ± 0.2	81.4 ± 0.6
Fraction G-8	21.6 ± 0.2	88.5 ± 0.4
Salidroside (1)	-	35.8 ± 2.5
EGCG dimer (2)	43.1 ± 0.4	37.7 ± 0.5
Rhodioloside B and C mixture (3, 4)	-	61.9 ± 3.0
Rosarin (5)	-	-
Cinnamyl alcohol (6)	27.7 ± 0.6	43.2 ± 1.5
Rhodiocyanoside A (7)	-	27.7 ± 4.8
Triandrin (8)	-	40.8 ± 3.5
Rosavin (9)	-	-
Tyrosol (10)	-	26.3 ± 0.7
Rosin (11)	-	-
Rosiridin (12)	16.2 ± 2.3	83.8 ± 1.1
L-Deprenyl ^a	36.0 ± 1.0	99.5 ± 0.2
Clorgyline ^a	100.0 ± 0.2	80.2 ± 0.9

^a Reference compound.

^b Inhibition lower than 15% was considered as inactive.





salidroside dose-dependently increases NPY expression^[31]

1.1 Support for feelings of well-being and mood

An *in vitro* study performed at the University of Camerino showed that a single oral administration of a Rhodiola extract led to significant improvements in mood-related behaviors in mice, indicating the potential of Rhodiola to promote feelings of well-being.^[33] Meanwhile, another study found that Rhodiola extract can help balance the activity of MAO enzymes, further demonstrating Rhodiola's potential for mood support.^[32] In a double-blind, placebo-controlled human study, researchers found that 42 days of Rhodiola extract supplementation 65 70% led to to improvements in feelings of well-being, indicating support for healthy mood states in the studied population.^[3] On the whole, volunteers supplementing with Rhodiola extract saw significant improvements in their mood states compared to placebo.^[3]

What's more, Rhodiola's main bioactive constituent, salidroside, has been shown to display a significant effect on mood.^{[34}] According to a study carried out by Panossian et the effects of a Rhodiola extract al., administered to rats in doses of 10, 20 and 50 mg/kg on mood and feelings of well-being were greater than the effects of the standard of care; moreover, salidroside and tyrosol isolated from the roots of Rhodiola were found to exhibit the most favorable effects on mood^[35]. The bottom line is that Rhodiola has shown promise in the area of mood support. The herb has gained increasing attention in the field of psychiatry, and additional research to evaluate its efficacy is

ongoing.

RhodioPrime 6X offers mood support		
At a Glance		
Publication	Zhu, L., et al., Salidroside attenuates lipopolysaccharide (LPS) induced serum cytokines and depressive-like behavior in mice. Neuroscience Letters, 2015. 606 : p. 1-6.	
Study Design	Comparison	
Participants	Mice	
Duration	5 days	
Intervention	Salidroside (12 mg/kg and 24 mg/kg) and fluoxetine (20 mg/kg) were administered intragastrically once daily for 5 days.	
Control	Untreated mice	
Key Findings	Salidroside increased brain-derived neurotrophic factor Salidroside decreased inflammation. Salidroside decreased depressive-like behavior.	

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1.2 Support for memory and cognitive function

Researchers found that oral supplementation with Rhodiola helped enhance memory in a dose- and time-dependent manner in healthy rats given a passive avoidance task.^[36] Another animal study found that Rhodiola extract may help improve learning and retention after 24 hours. The study also showed significant improvements in memory tests after 10-day treatment with the same dose of the extract.^[37] In a study performed at the University of Giessen, researchers assessed the efficacy of various Rhodiola extracts in a synaptic model of memory. Seven different Rhodiola extracts with different concentrations of rosavin and salidroside were obtained and studied. The study authors found that all variants were beneficial in terms of providing support for memory and cognition; furthermore, they found that the Rhodiola extracts containing both salidroside and rosavin promoted the best results. In simply comparing salidroside to rosavin, salidroside was more effective at lower concentrations, while rosavin was superior at higher concentrations.^[38] However, in isolated studies, salidroside has several benefits on its own, but rosavins have failed to yield any conclusive advantages when used alone.^[38] Along those lines, several studies have demonstrated that Rhodiola's biological properties in the central nervous system should be mainly attributed to salidroside, which has been shown to exert various adaptogenic functions; that is, salidroside seems to drive the most successful research. Both acute and consistent supplementation offers benefits;^[39] for instance, a single acute dose of salidroside

was also able to to provide support for memory and to help counteract feelings of overwhelm and despair in adult mice.^[21]

RhodioPrime 6X provides support for memory and healthy cognitive function		
At a Glance		
Publication	Jin, H., et al., Therapeutic Intervention of Learning and Memory Decays by Salidroside Stimulation of Neurogenesis in Aging. Mol Neurobiol, 2016. 53 (2): p. 851-866.	
Study Design	Comparison	
Participants	Adult mice at 4 months of age and old mice at 16 months of age	
Duration	5 days	
Intervention	Salidroside at different doses(1, 5, or 10 mg/kg per dose per day for 5 consecutive days)	
Control	Untreated mice	
Key Findings	Salidroside is effective against learning and memory decays via stimulation of CREB dependent functional neurogenesis in aging.	

1.3 Support for feelings of worry and anxiousness

Numerous studies have reported that Robiola may provide support for feelings of stress and anxiousness by promoting a healthy balance of neurotransmitters, namely serotonin.^[40, 41] For example, 10-20mg/kg of Rhodiola extract one hour prior to a light/dark exploration test was found to significantly, but not dose-dependently, improve mood- and stress-related behaviors in mice.^[33] In another research study, supplementation with a Rhodiola extract for 10 weeks led to a significant reduction in feelings of anxiousness and related behaviors.^[42] In an effort to better understand how Rhodiola achieves such effects, one study found that Rhodiola extract increased the protein content of the 5-HT1A receptor, which promote the production of can help serotonin.^[40] In another study, researchers found that Rhodiola extract helped reduce the activity of the 5-HT3 receptor,^[43] which is important considering this receptor is associated with increased feelings of worry and anxiety.^[44] According to the two studies, it seems that Rhodiola is able to provide



nutritional support that promotes healthy serotonin levels. Additionally, Rhodiola may provide further support for stress-related feelings of anxiousness by helping balance the activity of serotonin receptors.

RhodioPrime	6X provides support for anxious feelings
At a Glance	
Publication	Palmeri, A., et al., Salidroside, a Bioactive Compound of <u>Rhodiola</u> Rosea, Ameliorates Memory and Emotional Behavior in Adult Mice. Journal of Alzheimer's disease : JAD, 2016. 52 (1): p. 65-75.
Study Design	Comparison
Participants	Adult mice
Duration	A single i.p. administration
Intervention	Salidroside was diluted in PBS and stored at –20°C. Immediately prior to use, salidroside aliquots were diluted to reach a 25 mg/kg concentration. Mice were individually weighted and then treated by intraperitoneal (<u>i.p.</u>) injections 10 min before the behavioral test.
Control	Untreated mice
Key Findings	A single i.p. administration of salidroside in mice enhanced memory and exerts an antidepressant, and anxiolytic effect

1.4 Provides support when feeling mental fatigue and stress

Whether it's at the end of a long day of work, following an exhausting training session or being "under the gun" of a stressful situation, we may occasionally find ourselves battling fatigue. As an adaptogen, Rhodiola shows great potential in this area, as it has been shown to provide restorative, body-balancing support for stress-related fatigue.^[4, 45]

A double-blind and placebo-controlled study performed by Spasov et al, for example, examined the effects of 20 days of supplementation with 100mg Rhodiola extract in students during a stressful examination period. The result showed significant improvements in various indicators of acute, stress-induced fatigue, including cognition, fitness.^[46] clarity and physical mental Furthermore, another placebo-controlled study examined effects of Rhodiola the supplementation (either 370 mg or 555 mg) in college-aged students. Utilizing a proprietary

metric called an "anti-fatigue index," which measured multiple indicators of general lethargy, the researchers found that, compared to placebo, both levels of Rhodiola significantly improved mental and physical markers of fatigue.^[47] Meanwhile, another trial found that supplementation with Rhodiola extract led to a significant improvement in the Pines' burnout score for participants dealing with stressinduced fatigue ^[48]. Another open-label trial with Rhodiola extract at 400 mg daily for 4 weeks showed general benefits on perceived stress (questionnaire), improvements in stressinduced social and work dysfunction, and reductions in fatigue.^[49] Overall, these studies suggest that supplementation with Rhodiola extract is associated with improvements in mental fatigue associated with occasional stress.

To ascertain the mechanisms of action by which this adaptogen offers support for stressrelated fatigue, one study examined some biochemical markers for evaluating anti-stress effects in rabbits subjected to restraint stress. The researchers found that both salidroside and extracts of Rhodiola were strong inhibitors of stress-induced p-SAPK/p-JNK, suggesting a potential association between the adaptogen's potential to support feelings of well-being as well as its positive effects on mental performance under stress.^[50]

RhodioPrime 6X provides support for mental fatigue and stress		
At a Glance		
Publication	Panossian, A., et al., The adaptogens rhodiola and schizandra modify the response to immobilization stress in rabbits by suppressing the increase of phosphorylated stress-activated protein kinase, nitric oxide and cortisol. Drug target insights, 2007. 2: p. 39-54.	
Study Design	Comparison	
Participants	Male Chinchilla rabbits	
Duration	8 days	
Intervention	E. <u>senticosus</u> root extract -6.5 mg/kg, R. rosea root extract -1 mg/kg, S. chimensis berry extract -22 mg/kg; B. alba root extract -15 mg/kg, P. ginseng root extract -6 mg/kg, and salidroside -0.5 mg/kg.	
Control	Untreated mice	
Key Findings	Salidroside and extracts of S. chinensis and R. rosea were the most active inhibitors of stress-induced p-SAPK/p-JNK	



1.5 May help promote healthy appetite management

There's evidence to suggest that Rhodiola help promote healthy appetite may management and help provide support for cravings since there's a negative relationship between serotonin production and hunger and cravings.^[51] In a stress-induced eating model using mice, researchers administered a Rhodiola extract one hour prior to feeding to see whether the treatment would aid with appetite management and food intake. They found that the extract significantly reduced food intake, noting that the active principle salidroside, but not rosavin, dose-dependently decreased eating under the test conditions^[52], indicating that Rhodiola extracts may help curb appetite.

2. Support for Exercise and Physical Performance

Maintaining healthy energy levels is not only important in mental work settings but also in athletic performance. In 2004, a clinical trial tested the effect of four weeks of Rhodiola supplementation on exercise capacity. The twophase study showed that Rhodiola extract significantly increased time to exhaustion and VO₂ max, suggesting that Rhodiola can benefit athletic performance by helping improve energy levels and providing support for exercise-related fatigue thus improving endurance exercise performance.^[53] In another study, following supplementation with Rhodiola extract for 4 weeks, trained male athletes underwent a cardio-pulmonary exhaustion test and blood samples to evaluate exercise-related indications. The results showed that after an exhaustive exercise session, both lactate levels and

parameters of skeletal muscle damage were reduced in participants who supplemented with Rhodiola when compared to the placebotreated group. These results indicate that Rhodiola may enhance and optimize the ability to physical exercise.^[54] An additional study found a reduction in creatine kinase and Creactive protein after exhaustive exercise in healthy untrained volunteers supplementing with Rhodiola, when compared to placebo. These results demonstrate that Rhodiola extract may help mitigate the damage due to exhaustive exercise and also provide support for recovery from physical activity.^[55] Since intense exercise increases oxygen consumption and may produce an imbalance between reactive oxygen species (ROS) and antioxidants, it may lead to oxidative stress. Another animal study evaluated the effects of salidroside on exhaustive exerciseinduced oxidative stress in rats, and the results showed that salidroside was able to help raise exercise tolerance and increase the liver glycogen levels of the rats following exhaustive exercise. These results indicate that salidroside provides support for unhealthy levels of oxidative stress following exhaustive exercise.^[56]

What's more, Rhodiola may be associated with an increased VO₂ max and time to exhaustion with a reduction of creatine kinase and C-reactive protein. Moreover, in another study, researchers showed that salidroside was able to activate AMPK in skeletal muscle cells and increase glucose uptake in a concentrationdependent manner.^[57] This study also noted that insulin-induced glucose uptake was slightly enhanced with salidroside.^[57] Thus it seems that, in terms of physical performance, apart from the generally "feeling less tired," Rhodiola may also



contribute to promoting healthy energy levels by helping move nutrients to cells that need it.

RhodioPrime 6X provides support for exercise and physical performance.		
At a Glance		
Publication	Xu, J. and Y. Li, <i>Effects of salidroside on exhaustive exercise-induced oxidative stress in rats.</i> Mol Med Rep, 2012. 6 (5): p. 1195-8.	
Study Design	Comparison	
Participants	Rats	
Duration	4 weeks	
Intervention	Salidroside (25, 50 and 100 mg/kg, respectively) intragastrically (ig)	
Control	Untreated mice	
Key Findings	Salidroside was able to elevate the exercise tolerance and increase the liver glycogen levels of the rats following exhaustive exercise.	

3. Other potential interactions

3.1 May provide support for healthy carbohydrate metabolism

The potential negative effects of unhealthy carbohydrate management has been associated with accelerated aging,^[58] weight management issues,^[58] and a variety of other health issues.^[59] Carbohydrate metabolism concerns may stem from alterations in several pathways, including excessive accumulation of advanced glycation end-products (AGEs), which result from irreversible glycation of proteins.^[58] Salidroside has been shown to support a reduction in AGE formation in an accelerated mouse aging model induced by D-galactose.^[60] According to the study, salidroside helped mitigate increases in serum AGEs in some cases, and even more, the study found that salidroside may provide support for previous effects of AGEs in the neural and immune systems.^[60]

Though the relationship between AGEs and carbohydrate management remains to be further elucidated, another study did highlight the potential effects of Rhodiola on healthy metabolism carbohydrate in mice. The researchers found that administration of salidroside resulted in a time- and dosedependent effect on carbohydrate management.[61]

3.2 May promote organ health and function

Rhodiola may provide support for an array of body tissues and organs by way of its robust antioxidant capacity and by providing support for hypoxia.^[62] Hypoxia, which simply refers to deprivation, can be potentially oxygen dangerous and have long-term health repercussions when out of balance and improperly timed.^[63] Hypoxia inducible factor -1 (HIF-1), a key regulator in the body's response to hypoxic conditions, can help activate numerous transcription factors that regulate oxygen delivery and metabolic functioning.^[64] For example, HIF-1 appears to play a key role in the adaptive response to endurance exercise. Salidroside has been shown to promote healthy HIF-1 expression, which may, in turn, provide support for heart, liver, and kidney health and function.[64-66]

3.3 Support for healthy estrogen metabolism

There is evidence that Rhodiola extract may interact with the estrogen receptor without having any potentially negative estrogenic activity. Along these lines, Rhodiola has shown promise in providing support for complications associated menopause/perimenopause, such as fatigue, stress, feelings of well-being and cognitive performance.^[67]

Recommend dosage for RhodioPrime 6X

Rhodiola has a very low level of toxicity with mild side effects and no known interactions with drugs and other ingredients.^[68] In rat toxicity studies, the LD₅₀ (lethal dose at which 50% of animals die) was calculated to be 28.6 mL/kg, approximately 3360 mg/kg of body weight.^[69, 70]. Extrapolating that out to humans would equate

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to over 20,000 mg, depending on weight. With a suggested daily dose of 200 to 600 mg,^[68, 70] reaching a dose that high is extremely unlikely.

One more thing to be added when taking Rhodiola supplements is that one should be wary of the possible inaccurate labeling. A metaanalysis based on the studies of 39 Rhodiola products from multiple suppliers found that 23% of them contained no rosavin, which is a key marker that distinguishes Rhodiola rosea from other species of Rhodiola. Additionally, the meta-analysis found that two of the products did not contain any salidroside, indicating that some manufacturers are adulterating their products with other species of Rhodiola plants.^[71]

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