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REPORT

Reducing the Risks of High Cortisol

By Jan Whiticomb

Cortisol is a hormone that, when released in excess, can create a host of pathological conditions in the body.

When we are under stress or have an infection, cortisol raises our blood pressure and blood sugar. These changes help us survive short periods of stress, but they hurt us when they continue for years.

The problems associated with **chronically** elevated cortisol levels include:

- Suppressed immunity
- Hypertension
- High blood sugar (hyperglycemia)
- Insulin resistance
- Carbohydrate cravings
- Metabolic syndrome and type 2 diabetes
- Fat deposits on the face, neck, and belly
- Reduced libido
- Bone loss¹

Cortisol is a “stress hormone” that is responsible for many of the long-term health consequences suffered by those who encounter frequent stressful situations.

In this article, you will discover data about a natural remedy that reduces harmful cortisol levels. The benefits include improved **sleep quality, immunity, stress response, and organ function.**

THE DANGERS OF CORTISOL

Our bodies have a built-in mechanism for protecting us from the effects of acute, immediate stress (say, an attack by a wild animal). That effect, often called the “stress response,” involves production of several hormones in the adrenal gland. Following the immediate “adrenaline rush” that helps us escape the danger, we experience a massive release of cortisol, often referred to as the “stress hormone.”

Short-term bursts of cortisol are necessary to help us recover from the effects of stress. They boost blood sugar levels, providing immediate energy. They bolster immune responses in the short-term. They pull calcium from our bones, making it available to muscles for immediate action. They reduce our response to pain, keeping us focused on survival. And they enhance short-term memory, enabling us to evade similar threats in the near future.

Short, intermittent bursts of cortisol helped our ancestors survive in the wilderness and still come to our aid today. But unlike our ancestors, we face **chronically** stressful situations such as job loss and financial insecurity. Additionally, there are new biological stressors such as obesity and environmental toxins. This **chronic stress** means that we experience **chronic cortisol elevation**—where levels of the stress hormone never get a chance to return to normal. This produces a major problem that threatens our health and longevity.



The effects of chronic overexposure to cortisol can be devastating. Prolonged cortisol elevations result in sustained elevations of blood sugar, substantial loss of calcium from bones, depression of important immune responses, high blood pressure, loss of muscle mass, increased fat accumulation, and even loss of cognitive function.

If you've ever seen someone on chronic steroid therapy, say, for protection against transplant rejection, you've seen the destructive effects of cortisol: such people develop a classic "moon face," the result of excess fat and fluid accumulations. They develop a stooped posture, the result of calcium losses from bones. They often succumb to infections, the result of excessive immune suppression. Less obviously, but still of concern, they often develop dangerous hypertension requiring medication, and they can develop a range of cognitive dysfunctions as well.

So how can we preserve the beneficial effects of short-term cortisol elevations in response to acute, dangerous stress, while tamping down the dangerous effects of chronic, long-term cortisol elevations? That's where adaptogens such as rhodiola become important.

The reason that the Soviet scientists were so interested in rhodiola was that they recognized its value in situations where long-term stress was an issue. They saw that rhodiola's adaptogenic powers could balance the impairments produced by chronic stress without interfering with the valuable short-term stress response. Modern science is further validating rhodiola's ability to mitigate the impact of chronic cortisol elevations.

A large, phase III placebo-controlled clinical trial was conducted in Sweden in 2009, studying participants aged 20-55 years with a diagnosis of stress-related fatigue.² Subjects taking the rhodiola extract had significantly lower cortisol responses to chronic stress than did the placebo recipients—and as a result they had lower scores on scales of burnout and improved performance on cognitive testing.

WHAT YOU NEED TO KNOW: RHODIOLA: AN INCREASINGLY POPULAR ADAPTOGEN

Rhodiola is a known **adaptogen**—a plant-based compound that improves resistance to stress.

It exerts system-wide protective and restorative effects, increasing longevity and healthy life span in experimental models.

It has been shown to favorably modulate the stress response, restore vital organ function, and boost immunity.

It also combats aging cognitive function, minimizing depression, and anxiety.

Rhodiola enhances muscle performance, increases endurance, prevents muscle damage, and improves blood circulation.



A placebo-controlled Chinese study in 2009 also revealed protective effects of rhodiola on stress-induced cortisol levels in otherwise healthy individuals.³ In this case, subjects who received rhodiola experienced no change in their cortisol levels, while levels rose sharply among placebo recipients when both groups were exposed to chronic stress in the form of endurance exercise. Rhodiola also increased the efficiency with which subjects used oxygen, potentially reducing additional stress from oxygen radicals.

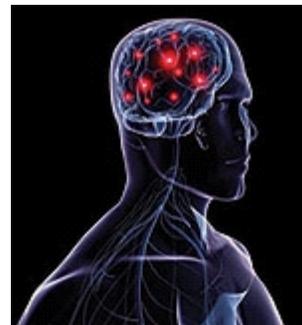
Advanced laboratory studies have now demonstrated that rhodiola achieves its cortisol-lowering, stress-fighting effects through several different mechanisms. Rhodiola directly interacts with the brain-adrenal gland system to reduce cortisol production while enhancing stress-resistance proteins.⁴ It upregulates "stress-sensor" proteins that reduce the production and impact of cortisol, resulting in enhanced mental and physical performance and even longevity.⁵ And multiple studies have demonstrated the complete lack of side effects from rhodiola supplementation.^{2,4}

MODULATING THE STRESS RESPONSE

Unlike any other compound, adaptogens condition your body to respond favorably to stress at the physiological level through a unique mechanism.

Adaptogens deliver minute shocks of mild stress that condition your physiology to respond to more major stresses in a favorable way. Interestingly, this is similar to the vaccine theory of inoculating the body with a small but harmless amount of a virus to help the body fend off a major attack.⁶

Rhodiola reduces fatigue and restores normal mental and physiological functioning, even in stressed humans categorized as having “burnout.”^{6,7} Studies of highly stressed individuals—doctors working overnight shifts, students studying for major exams—all demonstrate improvements in fatigue level, neuro-motor performance, and perceptive and cognitive function, even when tested under ongoing stressful conditions.⁸⁻¹⁰



A study of young to middle-aged women with significant impairment from living in psychologically stressful environments demonstrated improved scores on attention, speed, and accuracy during stressful cognitive tasks.¹¹ Those effects were evident just two hours after a single dose of rhodiola combined with Siberian ginseng and *Schisandra chinensis*. No serious side effects were reported in this or any other study of rhodiola.⁴

RHODIOLA RESEARCH CONDUCTED IN RUSSIA

Scarcely heard of in this country, rhodiola is an adaptogenic herb that first gained prominence when used by Russian cosmonauts to improve their endurance, concentration, and strength during space missions. During the Cold War, the Russians began to scientifically study the use of adaptogenic herbs for their elite athletes and military.

Their goal was to identify a natural product that created a sense of well being and reduced the harmful effects of the stress hormone, cortisol. The Russian scientists knew that high levels of cortisol initiate a dangerous cascade of stress and disease that would hamper the efforts of their best and brightest.

Rhodiola is one of only 16 scientifically established *adaptogens*, or plants endowed with the power to enhance system-wide function in the aging human.

A POWERFUL WEAPON AGAINST ANXIETY

While *Rhodiola rosea* has demonstrated the ability to help people deal with stress, it has also shown promise in alleviating stress-related symptoms such as anxiety and a diminished appetite.

A new study shined a light on rhodiola’s ability to circumvent the symptoms and severity of general anxiety disorder, a common condition characterized by frequent, excessive worry that is out of proportion to external circumstances. Symptoms of the disorder include difficulty concentrating, irritability, tense muscles, sleep disturbances, and trouble controlling worries. Ten participants (ages 34-55) with generalized anxiety disorder received a total daily dose of 340 mg of *R. rosea* extract for 10 weeks. At the study’s end, the participants demonstrated significant improvements in symptoms of generalized anxiety disorder, as determined by a widely used clinical assessment scale.¹²

As researchers began to investigate rhodiola in greater detail, they discovered that one of rhodiola’s key components, the phytochemical *salidroside*, may be responsible for many of rhodiola’s anti-aging properties, as well as an important factor in its ability to help combat anxiety. One animal study showed that salidroside produced notable sedative (calming) and hypnotic (sleep-inducing) effects in a dose-dependent fashion.¹³ Another study showed that administering salidroside to animals reversed stress-induced anorexia (discontinuation of eating).¹⁴ Together, these findings support rhodiola’s ability to calm individuals subjected to stress and to restore normal patterns of rest and eating.

These studies back up centuries of common knowledge in Russia and Scandinavia, where people have used rhodiola to alleviate everyday symptoms of anxiety and poor sleep.

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By Jan Whitcomb

ENHANCED LONGEVITY

Scientists have found that rhodiola possesses the power to *restore* malfunctioning biological systems, a key factor in reducing the detrimental effects of aging. In testing multiple organisms, rhodiola was found to enhance healthy responses to negative environmental stressors that include **oxidative stress**, **acute** and chronic heat shocks, and **toxic chemical exposure**.¹⁵

In the laboratory, rhodiola was found to protect human cells from premature aging when they were exposed to oxidative stress. Again, scientists used the compound derived from rhodiola called **salidroside**.¹⁶ Salidroside further preserves aging skin cells' ability to reproduce, thereby creating healthier, more vital skin. One group of scientists found that the salidroside in rhodiola dramatically diminishes pathologic symptoms of aging in laboratory mice by preventing accumulation of inflammatory *advanced glycation end products* (AGEs).¹⁷

Further bolstering rhodiola's anti-aging credentials is a recent study showing that rhodiola extract helps slow the aging process while extending life span.¹⁸ During this study, scientists administered rhodiola extract in the diet to a group of fruit flies. A control group did not receive the dietary rhodiola. The rhodiola-supplemented fruit flies demonstrated a 10% longer life span, compared with control subjects. When examined more closely, it was clear that the rhodiola-supplemented animals displayed *decelerated aging*, compared with subjects that did not receive the herb.¹⁹

Of important note, rhodiola's anti-aging and longevity-promoting effects appeared to be independent of any special diet.¹⁹ This is of vital importance because it suggests that rhodiola provides longevity benefits through a mechanism separate from caloric restriction, which, as *Life Extension* readers know, is the best-documented method to increase life span to date.²⁰

The possibility that rhodiola could act through a novel mechanism to forestall aging and lengthen life span is remarkable news for the anti-aging community.

BOLSTERING HEART HEALTH

Heart disease remains the number one killer, and doctors report that many cardiac events are stress induced.^{21,22}

Stress, whether physical or emotional, puts extra strain on the heart and other muscles. Numerous studies suggest that rhodiola exerts several protective benefits for the heart.²³

A probable link between the administration of *Rhodiola rosea* extract and prevention of arrhythmia (potentially dangerous abnormal heart rhythms) was discovered in a recent study.²⁴ The study involved test animals receiving *Rhodiola rosea* each day for 8 straight days. They were then subjected to an agent known to disrupt heart rhythm. Pre-treatment with rhodiola protected the animals against experimentally induced arrhythmia and electrical instability of the heart. The animals who received rhodiola were less vulnerable to heart damage caused by experimentally induced myocardial infarction (heart attack).

Another animal study highlights further potential cardioprotective benefits of rhodiola. In an animal model of coronary artery disease, rhodiola helped decrease the heart muscle's oxygen consumption while increasing oxygen supply to the myocardium, helping to ensure that the heart muscle has enough oxygen required for optimal function.²⁵

This evidence, combined with earlier animal studies suggesting rhodiola's ability to reduce cardiac stress-related damage,²³ supports the need for further in-depth studies of rhodiola's cardiovascular benefits in humans.



SYSTEM-WIDE AGE REVERSAL

Reduces Stress

Lowers levels of cortisol⁷
Restores normal physiological response to stress⁶⁴
Fights stress-induced despair⁶⁴

	Restores brain cells in areas damaged by stress-induced depression ^{45,46}
Protects the Heart	Prevents stress- and ischemia-induced heart muscle damage ⁶⁵⁻⁶⁷ Increases heart muscle cell tolerance to ischemia ⁶⁸ Prevents stress- and heart attack-induced arrhythmias ^{26,69-72} Reduces size of heart muscle infarction (tissue death) ^{62-64,68} Promotes new cardiac blood vessel growth after heart attack ^{66,73-75}
Protects the Liver	Prevents toxin- and oxidative stress-induced liver cell damage ²⁶⁻²⁹ Reduces serum markers of liver dysfunction ⁷⁶ Restores depleted liver stores of natural antioxidants ²⁶
Prevents Cancer	Inhibits proliferation of human leukemia cells ⁷⁷ Inhibits growth, induces death of human cancer cells ⁷⁸⁻⁸¹ Reduces new blood vessel formation (angiogenesis) in tumors ⁸²
Protects Against Radiation	Increases survival following otherwise lethal total-body irradiation ⁸³ Reduces radiation-induced lipid oxidation ⁸³ Scavenges radiation-induced free radicals ⁸³ Prevents anemia from red blood cell membrane damage ⁸³
Modulates the Immune System	Anti-inflammatory effects in settings of excessive inflammation ^{30,41} Stimulates appropriate immune responses ^{84,85} Boosts immune response to vaccines ³³ Antiviral effects against hepatitis C, influenza, and Coxsackie virus (cause of viral myocarditis) ³⁴⁻³⁶ Antibacterial effects against Staph aureus and tuberculosis ^{37,38} Combines with other adaptogens to boost suppressed immune function following chemotherapy ⁸⁶

VITAL ORGAN FUNCTION AND ENHANCED IMMUNITY

As the major detoxifier for the body, the liver processes countless amounts of toxins and removes them from our body. Rhodiola species support natural antioxidant systems in the liver and protect liver cells from damage by toxins and oxidative stress.²⁶⁻²⁹ As adaptogens, rhodiola species also carefully modulate the immune system, increasing its response to real threats of infection or malignancy, while preventing excessive inflammation.³⁰⁻³² A species of rhodiola was found to modulate the immune system to promote a healthy response to certain vaccinations.³³ Rhodiola potently inhibits tissue inflammatory responses to irritating drugs, preventing skin redness, swelling, and pain following exposure to the antifungal drug nystatin.³⁰

Rhodiola species possess direct antiviral and antibacterial activities, which may reduce the risk of serious infections.³⁴⁻³⁸ For example, Rhodiola rosea inhibits the enzymes that flu viruses use to attach to and invade the cells of the respiratory tract, reducing your chances of catching the flu following an exposure.³⁵

COMBATING BRAIN AGING

The neurodegeneration in Alzheimer's and Parkinson's diseases occurs as a result of inflammation in the nervous system coupled with the accumulation of harmful, pro-oxidant proteins that trigger even more inflammation and ultimately brain cell destruction. Constituents from rhodiola species such as salidroside display powerful antioxidant properties that prevent oxidative, pro-inflammatory effects as well as the formation of these proteins and the subsequent inflammatory cascade.³⁹⁻⁴³ Fewer brain cells die from oxidative stress.^{40,44}

Nerve cells in the memory centers of the brain resist age-related damage and produce more beneficial neurotransmitters after treatment with rhodiola.^{45,46}

Both short- and long-term memory enhancements have been demonstrated with rhodiola.⁴⁷⁻⁴⁹

Mental performance and acuity under experimentally induced adverse conditions, such as test-taking or sleep deprivation, are also significantly improved.^{7-9,11}

Rhodiola species help aging humans fall asleep faster, longer, and with improved quality of rest.^{50,51} In one study of men with sleep disturbances, rhodiola increased the amount of time spent in healthful REM sleep, reduced total wakeful time during the night, and markedly increased the "efficiency" of sleep sessions.⁵¹ Greater blood oxygenation during sleep was also observed—a key longevity factor.



WHAT IS AN “ADAPTOGEN?”

The concept of “adaptogens” is thousands of years old and is an important feature of ancient medical systems in the mountains of Asia and in northern Europe.⁸⁷ The modern term was coined in 1947 by a Russian scientist who defined an “adaptogen” as an agent that allows an organism to counteract and resist a variety of stressors.⁸⁸ In 2001, noted nutrition scientist Gregory S. Kelly updated and strengthened criteria for defining an adaptogen, requiring that any one adaptogen:⁸⁸

- Produce an increase in power of resistance against multiple stressors, including physical, chemical, or biological agents
- Normalize physiology, helping the body maintain youthful function, regardless of the cause of stress
- Normalize bodily functions beyond what is required to gain resistance to stress naturally.

Adaptogens exert a normalizing effect,⁸⁷ allowing organisms to increase healthy functions that are impaired by stress, and to decrease unhealthy responses that are triggered by stress, without any risk of “overshooting” and creating an unbalanced response. Scientists use the term “homeostasis” to describe your body’s ability to maintain physiological function within certain parameters, including temperature, respiratory rate, and blood chemistry within tightly controlled limits. In mainstream language, then, adaptogens simply enhance the body’s ability to maintain homeostasis and fight age-inducing stress.⁵

PHYSICAL PERFORMANCE

Physical activity and moderate exercise have multiple health benefits, but they also induce injury from oxidative stress, muscle cell damage, and inflammation. There is an important role, therefore, for adaptogens such as rhodiola in mitigating exercise-induced stress. Russian athletes have been known to use adaptogens to promote endurance and improve performance.

Rhodiola increased antioxidant blood levels and minimized oxidative stress-induced muscle damage in trained athletes for up to 24 hours after strenuous activity.^{52,53} One study showed an increase in the time to exhaustion during exercise, with significant increases in oxygen delivery to muscle tissues during the workout as well.⁵⁴



Rhodiola species have been used for centuries by villagers living high in the Himalayas to enhance their resistance to the effects of oxygen deprivation and to boost their endurance for strenuous tasks.⁵⁵ Those effects prove equally beneficial at more moderate altitudes. During exercise, rhodiola helps people work out longer, increasing their oxygen uptake and decreasing muscle damage.^{53,54} Long-term supplementation boosts energy storage capacity and blood oxygen level prior to exercise, further enhancing exercise capacity and endurance.⁵⁵

Rhodiola species protect internal organs from the low oxygen levels found at higher altitudes and that also occur during heart attacks and strokes.^{56,57} A 2011 study revealed something of even greater significance: rhodiola prevents a phenomenon known as *vascular remodeling* in lung tissue at high altitudes.⁵⁸

NOT ALL RHODIOLA IS THE SAME

The authentic *Rhodiola rosea* species validated in clinical research is wildcrafted from the forests of the Altai Mountains of Siberia. The raw materials are harvested after a minimum of four years of growth, according to the World Health Organization Guidelines of Good Agricultural Practices. This practice of sustainable stewardship preserves the natural resources of rhodiola’s native habitat.

Some rhodiola extracts are standardized to salidroside content only. Salidroside content is not specific to the Rhodiola genus only and is not the only beneficial constituent of rhodiola. Highly beneficial *Rhodiola rosea* extracts contain a ratio of rosavin and salidroside phytochemicals similar to that which is found in the authentic plant itself.

Vascular remodeling describes the thickening of pulmonary blood vessels that contributes to increased blood pressure in the lungs, a condition known as *pulmonary hypertension*.⁵⁹ Chronic exposure to high altitude is just one cause of this condition, which leads rapidly to congestive heart failure.^{60,61} More common causes of pulmonary hypertension include cardiovascular disease, obesity, and obstructive sleep apnea.^{59,62} Rhodiola’s ability to prevent vascular remodeling, then, may represent an important and sorely needed new approach to managing a major cause of death and disability in older adults.⁶³

SUMMARY

Rhodiola is a cortisol suppressing herb that is becoming an increasingly popular dietary intervention in the United States.

It is one of a handful of known **adaptogens**—plant-based compounds known to support long, healthy life span in part by exerting system-wide protective and restorative effects.

Rhodiola has been shown to favorably modulate the stress response, restore vital organ function, and boost immunity. It is a low-cost nutrient that combats cognitive dysfunction, minimizing depression and anxiety, while enhancing muscle performance, endurance, and circulatory health.



If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027.

References

1. Available at: <http://www.potbellysyndrome.com/documents/527EBBCC1397DBBF23868942BC34A88CBC0D78FF.html>. Accessed July 5, 2011.
2. Olsson EM, von Scheele B, Panossian AG. A randomised, double-blind, placebo-controlled, parallel-group study of the standardised extract shr-5 of the roots of *Rhodiola rosea* in the treatment of subjects with stress-related fatigue. *Planta Med.* 2009 Feb;75(2):105-12.
3. Zhang ZJ, Tong Y, Zou J, Chen PJ, Yu DH. Dietary supplement with a combination of *Rhodiola crenulata* and *Ginkgo biloba* enhances the endurance performance in healthy volunteers. *Chin J Integr Med.* 2009 Jun;15(3):177-83.
4. Panossian A, Wikman G, Sarris J. Rosenroot (*Rhodiola rosea*): traditional use, chemical composition, pharmacology and clinical efficacy. *Phytomedicine.* 2010 Jun;17(7):481-93.
5. Panossian A, Wikman G. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. *Curr Clin Pharmacol.* 2009 Sep;4(3):198-219.
6. Wiegant FA, Surinova S, Ytsma E, Langelaar-Makkinje M, Wikman G, Post JA. Plant adaptogens increase lifespan and stress resistance in *C. elegans*. *Biogerontology.* 2009 Feb;10(1):27-42.
7. Schutgens FW, Neogi P, van Wijk EP, van Wijk R, Wikman G, Wiegant FA. The influence of adaptogens on ultraweak biophoton emission: a pilot-experiment. *Phytother Res.* 2009 Aug;23(8):1103-8.
8. Shevtsov VA, Zholus BI, Shervarly VI, et al. A randomized trial of two different doses of a SHR-5 *Rhodiola rosea* extract versus placebo and control of capacity for mental work. *Phytomedicine.* 2003 Mar;10(2-3):95-105.
9. Spasov AA, Mandrikov VB, Mironova IA. The effect of the preparation rodakson on the psychophysiological and physical adaptation of students to an academic load. *Eksp Klin Farmakol.* 2000 Jan-Feb;63(1):76-8.
10. Darbinyan V, Kteyan A, Panossian A, Gabrielian E, Wikman G, Wagner H. *Rhodiola rosea* in stress induced fatigue--a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. *Phytomedicine.* 2000 Oct;7(5):365-71.
11. Aslanyan G, Amroyan E, Gabrielyan E, Nylander M, Wikman G, Panossian A. Double-blind, placebo-controlled, randomised study of single dose effects of ADAPT-232 on cognitive functions. *Phytomedicine.* 2010 Jun;17(7):494-9.
12. Bystritsky A, Kerwin L, Feusner JD. A Pilot Study of *Rhodiola rosea* (Rhodax((R))) for Generalized Anxiety Disorder (GAD). *J Altern Complement Med.* 2008 Mar;14(2):175-80.
13. Li T, Xu G, Wu L, Sun C. Pharmacological studies on the sedative and hypnotic effect of salidroside from the Chinese medicinal plant *Rhodiola sachalinensis*. *Phytomedicine.* 2007 Sep;14(9):601-4.
14. Mattioli L, Perfumi M. *Rhodiola rosea* L. extract reduces stress- and CRF-induced anorexia in rats. *J Psychopharmacol.*

15. Boon-Niermeijer EK, van den Berg A, Wikman G, Wiegant FA. Phyto-adaptogens protect against environmental stress-induced death of embryos from the freshwater snail *Lymnaea stagnalis*. *Phytomedicine*. 2000 Oct;7(5):389-99.
16. Mao GX, Wang Y, Qiu Q, et al. Salidroside protects human fibroblast cells from premature senescence induced by H₂O₂ partly through modulating oxidative status. *Mech Ageing Dev*. 2010 Nov-Dec;131(11-12):723-31.
17. Mao GX, Deng HB, Yuan LG, Li DD, Li YY, Wang Z. Protective role of salidroside against aging in a mouse model induced by D-galactose. *Biomed Environ Sci*. 2010 Apr;23(2):161-6.
18. Ohsugi M, Fan W, Hase K, et al. Active-oxygen scavenging activity of traditional nourishing-tonic herbal medicines and active constituents of *Rhodiola sacra*. *J Ethnopharmacol*. 1999 Oct;67(1):111-9.
19. Jafari M, Felgner JS, Bussel II, et al. *Rhodiola*: a promising anti-aging Chinese herb. *Rejuvenation Res*. 2007 Dec;10(4):587-602.
20. Medvedik O, Sinclair DA. Caloric restriction and life span determination of yeast cells. *Methods Mol Biol*. 2007;371:97-109.
21. Available at: <http://www.cdc.gov/features/heartmonth/>. Accessed July 1, 2011.
22. Available at: http://www.medicinenet.com/stress_and_heart_disease/article.htm. Accessed July 1, 2011.
23. Maslova L, Kondrafov B, Maslov L, Lishmanov I. The cardioprotective and antiadrenergic activity of an extract of *Rhodiola rosea* in stress. *Eksp Klin Farmakol*. 1994 Nov;57(6):61-3.
24. Maslov LN, Lishmanov IuB. Cardioprotective and antiarrhythmic properties of *Rhodiola roseae* preparations. *Eksp Klin Farmakol*. 2007 Sep-Oct;70(5):59-67.
25. Zhang ZH, Liu JS, Chu JN, et al. The effect of Hongjingtian (Gadol) injection on cardiac hemodynamics and myocardial oxygen consumption of dogs. *Zhongguo Zhong Yao Za Zhi*. 2005 Jul;30(13):1001-5.
26. Wu YL, Lian LH, Jiang YZ, Nan JX. Hepatoprotective effects of salidroside on fulminant hepatic failure induced by D-galactosamine and lipopolysaccharide in mice. *J Pharm Pharmacol*. 2009 Oct;61(10):1375-82.
27. Nakamura S, Li X, Matsuda H, et al. Bioactive constituents from Chinese natural medicines. XXVI. Chemical structures and hepatoprotective effects of constituents from roots of *Rhodiola sachalinensis*. *Chem Pharm Bull (Tokyo)*. 2007 Oct;55(10):1505-11.
28. Song EK, Kim JH, Kim JS, et al. Hepatoprotective phenolic constituents of *Rhodiola sachalinensis* on tacrine-induced cytotoxicity in Hep G2 cells. *Phytother Res*. 2003 May;17(5):563-5.
29. Udintsev SN, Krylova SG, Fomina TI. The enhancement of the efficacy of adriamycin by using hepatoprotectors of plant origin in metastases of Ehrlich's adenocarcinoma to the liver in mice. *Vopr Onkol*. 1992;38(10):1217-22.
30. Pooja, Bawa AS, Khanum F. Anti-inflammatory activity of *Rhodiola rosea*--"a second-generation adaptogen." *Phytother Res*. 2009 Aug;23(8):1099-102.
31. Abidov M, Grachev S, Seifulla RD, Ziegenfuss TN. Extract of *Rhodiola rosea* radix reduces the level of C-reactive protein and creatinine kinase in the blood. *Bull Exp Biol Med*. 2004 Jul;138(1):63-4.
32. Mishra KP, Padwad YS, Jain M, Karan D, Ganju L, Sawhney RC. Aqueous extract of *Rhodiola imbricata* rhizome stimulates proinflammatory mediators via phosphorylated I κ B and transcription factor nuclear factor- κ B. *Immunopharmacol Immunotoxicol*. 2006;28(2):201-12.
33. Mishra KP, Chanda S, Shukla K, Ganju L. Adjuvant effect of aqueous extract of *Rhodiola imbricata* rhizome on the immune responses to tetanus toxoid and ovalbumin in rats. *Immunopharmacol Immunotoxicol*. 2010 Mar;32(1):141-6.
34. Wang H, Ding Y, Zhou J, Sun X, Wang S. The in vitro and in vivo antiviral effects of salidroside from *Rhodiola rosea* L. against

coxsackievirus B3. *Phytomedicine*. 2009 Mar;16(2-3):146-55.

35. Jeong HJ, Ryu YB, Park SJ, et al. Neuraminidase inhibitory activities of flavonols isolated from *Rhodiola rosea* roots and their in vitro anti-influenza viral activities. *Bioorg Med Chem*. 2009 Oct 1;17(19):6816-23.

36. Zuo G, Li Z, Chen L, Xu X. Activity of compounds from Chinese herbal medicine *Rhodiola kirilowii* (Regel) Maxim against HCV NS3 serine protease. *Antiviral Res*. 2007 Oct;76(1):86-92.

37. Wong YC, Zhao M, Zong YY, Chan CY, Che CT. Chemical constituents and anti-tuberculosis activity of root of *Rhodiola kirilowii*. *Zhongguo Zhong Yao Za Zhi*. 2008 Jul;33(13):1561-5.

38. Ming DS, Hillhouse BJ, Guns ES, et al. Bioactive compounds from *Rhodiola rosea* (Crassulaceae). *Phytother Res*. 2005 Sep;19(9):740-3.

39. Mook-Jung I, Kim H, Fan W, et al. Neuroprotective effects of constituents of the oriental crude drugs, *Rhodiola sacra*, *R. sachalinensis* and Tokaku-joki-to, against beta-amyloid toxicity, oxidative stress and apoptosis. *Biol Pharm Bull*. 2002 Aug;25(8):1101-4.

40. Zhang L, Yu H, Sun Y, et al. Protective effects of salidroside on hydrogen peroxide-induced apoptosis in SH-SY5Y human neuroblastoma cells. *Eur J Pharmacol*. 2007 Jun 14;564(1-3):18-25.

41. Chen X, Zhang Q, Cheng Q, Ding F. Protective effect of salidroside against H₂O₂-induced cell apoptosis in primary culture of rat hippocampal neurons. *Mol Cell Biochem*. 2009 Dec;332(1-2):85-93.

42. Bocharov EV, Ivanova-Smolenskaya IA, Poleshchuk VV, Kucheryanu VG, Il'enko VA, Bocharova OA. Therapeutic efficacy of the neuroprotective plant adaptogen in neurodegenerative disease (Parkinson's disease as an example). *Bull Exp Biol Med*. 2010 Nov;149(6):682-4.

43. Zhang L, Yu H, Zhao X, et al. Neuroprotective effects of salidroside against beta-amyloid-induced oxidative stress in SH-SY5Y human neuroblastoma cells. *Neurochem Int*. 2010 Nov;57(5):547-55.

44. Zhang WS, Zhu LQ, Niu FL, Deng RC, Ma CX. Protective effects of salidroside on injury induced by hypoxia/hypoglycemia in cultured neurons. *Zhongguo Zhong Yao Za Zhi*. 2004 May;29(5):459-62.

45. Qin YJ, Zeng YS, Zhou CC, Li Y, Zhong ZQ. Effects of *Rhodiola rosea* on level of 5-hydroxytryptamine, cell proliferation and differentiation, and number of neuron in cerebral hippocampus of rats with depression induced by chronic mild stress. *Zhongguo Zhong Yao Za Zhi*. 2008 Dec;33(23):2842-6.

46. Chen QG, Zeng YS, Qu ZQ, et al. The effects of *Rhodiola rosea* extract on 5-HT level, cell proliferation and quantity of neurons at cerebral hippocampus of depressive rats. *Phytomedicine*. 2009 Sep;16(9):830-8.

47. Panossian A, Wagner H. Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration. *Phytother Res*. 2005 Oct;19(10):819-38.

48. Walker TB, Robergs RA. Does *Rhodiola rosea* possess ergogenic properties? *Int J Sport Nutr Exerc Metab*. 2006 Jun;16(3):305-15.

49. Hung SK, Perry R, Ernst E. The effectiveness and efficacy of *Rhodiola rosea* L.: a systematic review of randomized clinical trials. *Phytomedicine*. 2011 Feb 15;18(4):235-44.

50. Li T, Xu G, Wu L, Sun C. Pharmacological studies on the sedative and hypnotic effect of salidroside from the Chinese medicinal plant *Rhodiola sachalinensis*. *Phytomedicine*. 2007 Sep;14(9):601-4.

51. Ha Z, Zhu Y, Zhang X, et al. The effect of *rhodiola* and acetazolamide on the sleep architecture and blood oxygen saturation in men living at high altitude. *Zhonghua Jie He He Hu Xi Za Zhi*. 2002 Sep;25(9):527-30.

52. Skarpanska-Stejnborn A, Pilaczynska-Szczesniak L, Basta P, Deskur-Smielecka E. The influence of supplementation with *Rhodiola rosea* L. extract on selected redox parameters in professional rowers. *Int J Sport Nutr Exerc Metab*. 2009 Apr;19(2):186-99.

53. Parisi A, Tranchita E, Duranti G, et al. Effects of chronic *Rhodiola Rosea* supplementation on sport performance and antioxidant capacity in trained male: preliminary results. *J Sports Med Phys Fitness*. 2010 Mar;50(1):57-63.
54. De Bock K, Eijnde BO, Ramaekers M, Hespel P. Acute *Rhodiola rosea* intake can improve endurance exercise performance. *Int J Sport Nutr Exerc Metab*. 2004 Jun;14(3):298-307.
55. Zhang ZH, Feng SH, Hu GD, Cao ZK, Wang LY. Effect of *Rhodiola kirilowii* (Regel.) Maxim on preventing high altitude reactions. A comparison of cardiopulmonary function in villagers at various altitudes. *Zhongguo Zhong Yao Za Zhi*. 1989 Nov;14(11):687-90, 704.
56. Lee FT, Kuo TY, Liou SY, Chien CT. Chronic *Rhodiola rosea* extract supplementation enforces exhaustive swimming tolerance. *Am J Chin Med*. 2009;37(3):557-72.
57. Zhang Z, Wang L, Chen Q, et al. Electron microscopic observation of the effects of *Rhodiola kirilowii* (Regel.) Maxim. in preventing damage of the rat viscera by a hypoxic high altitude environment. *Zhongguo Zhong Yao Za Zhi*. 1990 Mar;15(3):177-81, 92.
58. Bai MK, Guo Y, Bian BD, et al. Integripetal *rhodiola* herb attenuates high altitude-induced pulmonary arterial remodeling and expression of vascular endothelial growth factor in rats. *Sheng Li Xue Bao*. 2011 Apr 25;63(2):143-48.
59. Kayikcioglu M. The etiopathogenesis of pulmonary hypertension: inflammation, vascular remodeling. *Anadolu Kardiyol Derg*. 2010 Aug;10 Suppl 1:5-8.
60. Guglin M, Khan H. Pulmonary hypertension in heart failure. *J Card Fail*. 2010 Jun;16(6):461-74.
61. Leon-Velarde F, Villafuerte FC, Richalet JP. Chronic mountain sickness and the heart. *Prog Cardiovasc Dis*. 2010 May-Jun;52(6):540-9.
62. Arbuzov AG, Krylatov AV, Maslov LN, Burkova VN, Naryzhnaya NV. Antihypoxic, cardioprotective, and antifibrillation effects of a combined adaptogenic plant preparation. *Bull Exp Biol Med*. 2006 Aug;142(2):212-5.
63. Stenmark KR, Rabinovitch M. Emerging therapies for the treatment of pulmonary hypertension. *Pediatr Crit Care Med*. 2010 Mar;11(2 Suppl):S85-90.
64. Panossian A, Nikoyan N, Ohanyan N, et al. Comparative study of *Rhodiola* preparations on behavioral despair of rats. *Phytomedicine*. 2008 Jan;15(1-2):84-91.
65. Maslov LN, Lishmanov Iu B. Cardioprotective and antiarrhythmic properties of *Rhodiolae roseae* preparations. *Eksp Klin Farmakol*. 2007 Sep-Oct;70(5):59-67.
66. Zhang J, Liu A, Hou R, Jia X, Jiang W, Chen J. Salidroside protects cardiomyocyte against hypoxia-induced death: a HIF-1 α -activated and VEGF-mediated pathway. *Eur J Pharmacol*. 2009 Apr 1;607(1-3):6-14.
67. Zhong H, Xin H, Wu LX, Zhu YZ. Salidroside attenuates apoptosis in ischemic cardiomyocytes: a mechanism through a mitochondria-dependent pathway. *J Pharmacol Sci*. 2010;114(4):399-408.
68. Wu T, Zhou H, Jin Z, et al. Cardioprotection of salidroside from ischemia/reperfusion injury by increasing N-acetylglucosamine linkage to cellular proteins. *Eur J Pharmacol*. 2009 Jun 24;613(1-3):93-9.
69. Lishmanov Iu B, Maslova LV, Maslov LN, Dan'shina EN. The anti-arrhythmia effect of *Rhodiola rosea* and its possible mechanism. *Biull Eksp Biol Med*. 1993 Aug;116(8):175-6.
70. Maimeskulova LA, Maslov LN, Lishmanov Iu B, Krasnov EA. The participation of the mu-, delta- and kappa-opioid receptors in the realization of the anti-arrhythmia effect of *Rhodiola rosea*. *Eksp Klin Farmakol*. 1997 Jan-Feb;60(1):38-9.
71. Maimeskulova LA, Maslov LN. The anti-arrhythmia action of an extract of *Rhodiola rosea* and of n-tyrosol in models of experimental arrhythmias. *Eksp Klin Farmakol*. 1998 Mar-Apr;61(2):37-40.
72. Maslov LN, Lishmanov YB, Arbuzov AG, et al. Antiarrhythmic activity of phytoadaptogens in short-term ischemia-reperfusion

of the heart and postinfarction atherosclerosis. *Bull Exp Biol Med*. 2009 Mar;147(3):331-4.

73. Arbuzov AG, Maslov LN, Burkova VN, Krylatov AV, Konkovskaia Iu N, Safronov SM. Phytoadaptogens-induced phenomenon similar to ischemic preconditioning. *Russ Fiziol Zh Im I M Sechenova*. 2009 Apr;95(4):398-404.

74. Li J, Fan WH, Ao H. Effect of rhodiola on expressions of Flt-1, KDR and Tie-2 in rats with ischemic myocardium. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 2005 May;25(5):445-8.

75. Gao XF, Shi HM, Sun T, Ao H. Effects of Radix et Rhizoma Rhodiolae Kirilowii on expressions of von Willebrand factor, hypoxia-inducible factor 1 and vascular endothelial growth factor in myocardium of rats with acute myocardial infarction. *Zhong Xi Yi Jie He Xue Bao*. 2009 May;7(5):434-40.

76. Iaremii IN, Grigor'eva NF. Hepatoprotective properties of liquid extract of *Rhodiola rosea*. *Eksp Klin Farmakol*. 2002 Nov-Dec;65(6):57-9.

77. Mishra KP, Padwad YS, Dutta A, et al. Aqueous extract of *Rhodiola imbricata* rhizome inhibits proliferation of an erythroleukemic cell line K-562 by inducing apoptosis and cell cycle arrest at G2/M phase. *Immunobiology*. 2008;213(2):125-31.

78. Tu Y, Roberts L, Shetty K, Schneider SS. *Rhodiola crenulata* induces death and inhibits growth of breast cancer cell lines. *J Med Food*. 2008 Sep;11(3):413-23.

79. Hu X, Lin S, Yu D, Qiu S, Zhang X, Mei R. A preliminary study: the anti-proliferation effect of salidroside on different human cancer cell lines. *Cell Biol Toxicol*. 2010 Dec;26(6):499-507.

80. Hu X, Zhang X, Qiu S, Yu D, Lin S. Salidroside induces cell-cycle arrest and apoptosis in human breast cancer cells. *Biochem Biophys Res Commun*. 2010 Jul 16;398(1):62-7.

81. Liu Z, Li X, Simoneau AR, Jafari M, Zi X. *Rhodiola rosea* and salidroside decrease the growth of bladder cancer cell lines via inhibition of the mTOR pathway and induction of autophagy. *Mol Carcinog*. 2011 Apr 22.

82. Skopinska-Rozewska E, Malinowski M, Wasutynski A, et al. The influence of *Rhodiola quadrifida* 50% hydro-alcoholic extract and salidroside on tumor-induced angiogenesis in mice. *Pol J Vet Sci*. 2008;11(2):97-104.

83. Arora R, Chawla R, Sagar R, et al. Evaluation of radioprotective activities *Rhodiola imbricata* Edgew--a high altitude plant. *Mol Cell Biochem*. 2005 May;273(1-2):209-23.

84. Mishra KP, Ganju L, Chanda S, Karan D, Sawhney RC. Aqueous extract of *Rhodiola imbricata* rhizome stimulates Toll-like receptor 4, granzyme-B and Th1 cytokines in vitro. *Immunobiology*. 2009;214(1):27-31.

85. Li HX, Sze SC, Tong Y, Ng TB. Production of Th1- and Th2-dependent cytokines induced by the Chinese medicine herb, *Rhodiola algida*, on human peripheral blood monocytes. *J Ethnopharmacol*. 2009 Jun 22;123(2):257-66.

86. Kormosh N, Laktionov K, Antoshechkina M. Effect of a combination of extract from several plants on cell-mediated and humoral immunity of patients with advanced ovarian cancer. *Phytother Res*. 2006 May;20(5):424-5.

87. Rege NN, Thatte UM, Dahanukar SA. Adaptogenic properties of six rasayana herbs used in Ayurvedic medicine. *Phytother Res*. 1999 Jun;13(4):275-91.

88. Kelly GS. *Rhodiola rosea*: a possible plant adaptogen. *Altern Med Rev*. 2001 Jun;6(3):293-302.

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