

12 July 2011
EMA/HMPC/232102/2011
Committee on Herbal Medicinal Products (HMPC)

List of references supporting the assessment of *Rhodiola rosea L., rhizoma et radix*

Draft

The Agency acknowledges that copies of the underlying works used to produce this monograph were provided for research only with exclusion of any commercial purpose.

Abidov M, Crendal F, Grachev S, Seifulla R, Ziegenfuss T. Effect of extracts from Rhodiola rosea and Rhodiola crenulata (Crassulaceae) roots on ATP content in mitochondria of skeletal muscles. Bull Exp Biol Med 2003, 136(6):585-7.

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, 138(1):63-4.

Ali Z, Fronczek FR, Khan IA. Phenylalkanoids and monoterpane analogues from the roots of Rhodiola rosea. Planta Med 2008; 74: 178-81.

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. Phytomed 2010, 17(7): 494-9.

Battistelli M, De Sanctis R, De Bellis R, Cucchiarini L, Dacha M, Gobbi P. Rhodiola rosea as antioxidant in red blood cells: ultrastructural and haemolytic behaviour. Eur J Histochem 2005, 49(3):243-54.

Blomkvist J, Taube A, Larhammar D. Perspective on Roseroot (Rhodiola rosea) studies. Planta Med 2009, 75(11):1187-90.

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*. Phytomed 2000, 7(5):389-99.

Bystritsky A, Kerwin L, Feusner JD. A pilot study of Rhodiola rosea (Rhodax) for generalized anxiety disorder (GAD). J Altern Complement Med 2008, 14(2):175-80.

Calcabrini C, De Bellis R, Mancini U, Cucchiarini L, Potenza L, De Sanctis R, Patrone V, Scesa C, Dacha M. Rhodiola rosea ability to enrich cellular antioxidant defences of cultured human keratinocytes. Arch Dermatol Res 2010, 302(3):191-200.



Cao LL, Du GH, Wang MW. The effect of salidroside on cell damage induced by glutamate and intracellular free calcium in PC12 cells. *J Asian Nat Prod Res* 2006, 8(1-2):159-65.

Chen QG, Zeng YS, Tang JY, Qin YJ, Chen SJ, Zhong ZQ. Effects of Rhodiola rosea on body weight and intake of sucrose and water in depressive rats induced by chronic mild stress. *Zhong Xi Yi Jie He Xue Bao* 2008a, 6(9):952-5.

Chen QG, Zeng YS, Qu ZQ, Tang JY, Qin YJ, Chung P, Wong R, Hägg U. The effects of Rhodiola rosea extract on 5-HT level, cell proliferation and quantity of neurons at cerebral hippocampus of depressive rats. *Phytomed* 2009, 16(9):830-8.

Chen TS, Liou SY, Chang YL. Antioxidant evaluation of three adaptogen extracts. *Am J Chin Med* 2008, 36(6):1209-17.

Chen X, Liu J, Gu X, Ding F. Salidroside attenuates glutamate-induced apoptotic cell death in primary cultured hippocampal neurons of rats. *Brain Res* 2008b, 1238: 189-198.

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* 2009a, 332(1-2):85-93.

Cifani C, Micioni Di B MV, Vitale G, Ruggieri V, Ciccioppo R, Massi M. Effect of salidroside, active principle of Rhodiola rosea extract, on binge eating. *Physiol Behav* 2010, 101(5):555-62.

Colson SN, Wyatt FB, Johnston DL, Autrey LD, FitzGerald YL, Earnest CP. Cordyceps sinensis- and Rhodiola rosea-based supplementation in male cyclists and its effect on muscle tissue oxygen saturation. *J Strength Cond Res* 2005, 19(2):358-63.

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. *Phytomed* 2000, 7(5):365-71.

Darbinyan V, Aslanyan G, Amroyan E, Gabrielyan E, Malmström C, Panossian A. Clinical trial of Rhodiola rosea L. extract SHR-5 in the treatment of mild to moderate depression. *Nord J Psychiatry* 2007, 61(5):343-8.

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, 14(3):298-307.

De Sanctis R, De Bellis R, Scesa C, Mancini U, Cucchiari L, Dacha M. In vitro protective effect of Rhodiola rosea extract against hypochlorous acid-induced oxidative damage in human erythrocytes. *Biofactors* 2004, 20(3):147-59.

Dieamant Gde C, Velazquez Pereda Mdel C, Eberlin S, Nogueira C, Werka RM, Queiroz ML. Neuroimmunomodulatory compound for sensitive skin care: in vitro and clinical assessment. *J Cosmet Dermatol* 2008, 7(2):112-9.

Evdokimov VG. Effect of cryopowder Rhodiola rosae L. on cardiorespiratory parameters and physical performance of humans. *Aviakosm Ekolog Med* 2009, 43(6):52-6.

Evstatieva L, Todorova M, Antonova D, Staneva J. Chemical composition of the essential oils of Rhodiola rosea L. of three different origins. *Pharmacogn Mag* 2010, 6(24):256-8.

Fintelmann V, Gruenwald J. Efficacy and tolerability of a Rhodiola rosea extract in adults with physical and cognitive deficiencies. *Adv Ther* 2007, 24(4):929-39.

Ha Z, Zhu Y, Zhang X, Cui J, Zhang S, Ma Y, Wang W, Jian X. 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, 25(9):527-30.

Hellum BH, Tosse A, Hoybakk K, Thomsen M, Rohloff J, Georg Nilsen O. Potent in vitro inhibition of CYP3A4 and P-glycoprotein by Rhodiola rosea. *Planta Med* 2010, 76(4):331-8.

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, 398(1):62-7.

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* 2010a, 26(6):499-507.

Hung SK, Perry R, Ernst E. The effectiveness and efficacy of Rhodiola rosea L.: A systematic review of randomized clinical trials. *Phytomed* 2011, 18(4):235-44.

Huang SC, Lee FT, Kuo TY, Yang JH, Chien CT. Attenuation of long-term Rhodiola rosea supplementation on exhaustive swimming-evoked oxidative stress in the rat. *Chin J Physiol* 2009, 52(5):316-24.

Iovieno N, Dalton ED, Fava M, Mischoulon D. Second-tier natural antidepressants: Review and critique. *J Affect Disord* 2010, Jun 24. [Epub ahead of print]

Ip SP, Che CT, Leung PS. Association of free radicals and the tissue renin-angiotensin system: prospective effects of Rhodiola, a genus of Chinese herb, on hypoxia-induced pancreatic injury. *J Pancreas* 2001, 2(1):16-25.

Jafari M, Felgner JS, Bussel II, Hutchili T, Khodayari B, Rose MR, Vince-Cruz C, Mueller LD. Rhodiola: a promising anti-aging Chinese herb. *Rejuvenation Res* 2007, 10(4):587-602.

Jeong HJ, Ryu YB, Park SJ, Kim JH, Kwon HJ, Kim JH, Park KH, Rho MC, Lee WS. Neuraminidase inhibitory activities of flavonols isolated from Rhodiola rosea roots and their in vitro anti-influenza viral activities. *Bioorg Med Chem* 2009, 17(19):6816-23.

Kim SH, Hyun SH, Choung SY. Antioxidative effects of Cinnamomi cassiae and Rhodiola rosea extracts in liver of diabetic mice. *Biofactors* 2006, 26(3):209-19.

Kobayashi K, Yamada K, Murata T, Hasegawa T, Takano F, Koga K, Fushiya S, Batkhuu J, Yoshizaki F. Constituents of Rhodiola rosea showing inhibitory effect on lipase activity in mouse plasma and alimentary canal. *Planta Med* 2008, 74(14):1716-9.

Kucinskaite A, Poblocka-Olech L, Krauze-Baranowska M, Sznitowska M, Savickas A, Briedis V. Evaluation of biologically active compounds in roots and rhizomes of Rhodiola rosea L. cultivated in Lithuania. *Medicina (Kaunas)* 2007, 43(6):487-94.

Kwon YI, Jang HD, Shetty K. Evaluation of Rhodiola crenulata and Rhodiola rosea for management of type II diabetes and hypertension. *Asia Pac J Clin Nutr* 2006, 15(3):425-32.

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.

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, 25(5):445-8.

Li HB, Ge YK, Zheng XX, Zhang L. Salidroside stimulated glucose uptake in skeletal muscle cells by activating AMP-activated protein kinase. *Eur J Pharmacol* 2008, 588(2-3):165-9.

Li X, Ye X, Li X, Sun X, Liang Q, Tao L, Kang X, Chen J. Salidroside protects against MPP(+) -induced apoptosis in PC12 cells by inhibiting the NO pathway. *Brain Res.* 2011, Jan 14. [Epub ahead of print]

Majewska A, Hoser G, Furmanowa M, Urbanska N, Pietrosiuk A, Zobel A, Kuras M. Antiproliferative and antimitotic effect, S phase accumulation and induction of apoptosis and necrosis after treatment of extract from Rhodiola rosea rhizomes on HL-60 cells. *J Ethnopharmacol* 2006, 103(1):43-52.

Mao GX, Wang Y, Qiu Q, Deng HB, Yuan LG, Li RG, Song DQ, Li YY, Li DD, Wang Z. Salidroside protects human fibroblast cells from premature senescence induced by H₂O₂ partly through modulating oxidative status. *Mech Ageing Dev* 2010, 131(11-12):723-31.

Maslov LN, Lishmanov YB. Cardioprotective and antiarrhythmic properties of Rhodiola roseae preparations. *Eksp Klin Farmakol* 2007, 70(5):59-67.

Maslov LN, Lishmanov YB, Arbuzov AG, Krylatov AV, Budankova EV, Konkovskaya YN, Burkova VN, Severova EA. Antiarrhythmic activity of phytoadaptogens in short-term ischemia-reperfusion of the heart and postinfarction cardiosclerosis. *Bull Exp Biol Med* 2009, 147(3):331-4.

Mattioli L, Perfumi M. Rhodiola rosea L. extract reduces stress- and CRF-induced anorexia in rats. *J Psychopharmacol* 2007, 21(7):742-50.

Mattioli L, Funari C, Perfumi M. Effects of Rhodiola rosea L. extract on behavioural and physiological alterations induced by chronic mild stress in female rats. *J Psychopharmacol* 2009, 23(2):130-42.

Mattioli L, Perfumi M. Evaluation of Rhodiola rosea L. extract on affective and physical signs of nicotine withdrawal in mice. *J Psychopharmacol* 2011, 25(3):402-410.

Mattioli L, Perfumi M. Effects of a Rhodiola rosea L. extract on acquisition and expression of morphine tolerance and dependence in mice. *J Psychopharmacol* 2011a, 25(3): 411-420.

Ming DS, Hillhouse BJ, Guns ES, Eberding A, Xie S, Vimalanathan S, Towers GH. Bioactive compounds from Rhodiola rosea (Crassulaceae). *Phytother Res* 2005, 19(9):740-3.

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, 75(2):105-12.

Panossian A, Hovhannisyan A, Abrahamyan H, Gabrielyan E, Wikman G. Pharmacokinetic and pharmacodynamic study of interaction of Rhodiola rosea SHR-5 extract with warfarin and theophylline in rats. *Phytother Res* 2009a, 23(3):351-7.

Panossian A, Nikoyan N, Ohanyan N, Hovhannisyan A, Abrahamyan H, Gabrielyan E, Wikman G. Comparative study of Rhodiola preparations on behavioral despair of rats. *Phytomed* 2008, 15(1-2):84-91.

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

Panossian A, Wikman G. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. *Curr Clin Pharmacol* 2009, 4(3):198-219.

Panossian A, Wikman G, Kaur P, Asea A. Adaptogens exert a stress-protective effect by modulation of expression of molecular chaperones. *Phytomed* 2009, 16(6-7):617-22.

Panossian A, Wikman G, Sarris J. Rosenroot (*Rhodiola rosea*): traditional use, chemical composition, pharmacology and clinical efficacy. *Phytomed* 2010, 17(7):481-93.

- Parisi A, Tranchita E, Duranti G, Ciminelli E, Quaranta F, Ceci R, Cerulli C, Borrione P, Sabatini S. Effects of chronic Rhodiola Rosea supplementation on sport performance and antioxidant capacity in trained male: preliminary results. *J Sports Med Phys Fitness* 2010, 50(1):57-63.
- Perfumi M, Mattioli L. Adaptogenic and central nervous system effects of single doses of 3% rosavin and 1% salidroside Rhodiola rosea L. extract in mice. *Phytother Res* 2007, 21(1):37-43.
- Pooja, Bawa AS, Khanum F. Anti-inflammatory activity of Rhodiola rosea--"a second-generation adaptogen". *Phytother Res* 2009, 23(8):1099-102.
- Provalova NV, Skurikhin EG, Pershina OV, Suslov NI, Minakova MY, Dygai AM, Gol'dberg ED. Mechanisms underling the effects of adaptogens on erythropoiesis during paradoxical sleep deprivation. *Bull Exp Biol Med* 2002, 133(5):428-32.
- Qian EW, Ge DT, Kong SK. Salidroside promotes erythropoiesis and protects erythroblasts against oxidative stress by up-regulating glutathione peroxidase and thioredoxin. *J Ethnopharmacol* 2011, 133(2):308-14.
- 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, 33(23):2842-6.
- Qu ZQ, Zhou Y, Zeng YS, Li Y, Chung P. Pretreatment with Rhodiola rosea extract reduces cognitive impairment induced by intracerebroventricular streptozotocin in rats: implication of anti-oxidative and neuroprotective effects. *Biomed Environ Sci* 2009, 22(4):318-26.
- Ouyang JF, Lou J, Yan C, Ren ZH, Qiao HX, Hong DS. In-vitro promoted differentiation of mesenchymal stem cells towards hepatocytes induced by salidroside. *J Pharm Pharmacol* 2010, 62(4):530-8.
- Rohloff J. Volatiles from rhizomes of Rhodiola rosea L. *Phytochem* 2002, 59(6):655-61.
- Saratikov AS. The golden root (Rhodiola rosea). Tomsk University Publishers, Tomsk 1974.
- Sarris J. Herbal medicines in the treatment of psychiatric disorders: a systematic review. *Phytother Res* 2007, 21(8):703-16.
- Schriner SE, Abrahamyan A, Avanessian A, Bussel I, Maler S, Gazarian M, Holmbeck MA, Jafari M. Decreased mitochondrial superoxide levels and enhanced protection against paraquat in Drosophila melanogaster supplemented with Rhodiola rosea. *Free Radic Res* 2009, 43(9):836-43.
- Schriner SE, Avanesian A, Liu Y, Luesch H, Jafari M. Protection of human cultured cells against oxidative stress by Rhodiola rosea without activation of antioxidant defenses. *Free Radic Biol Med* 2009a, 47(5):577-84.
- 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, 23(8):1103-8.
- Shen W, Fan WH, Shi HM. Effects of rhodiola on expression of vascular endothelial cell growth factor and angiogenesis in aortic atherosclerotic plaque of rabbits. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2008, 28(11):1022-5.
- Shevtsov VA, Zholus BI, Shervarly VI, Vol'skij VB, Korovin YP, Khristich MP, Roslyakova NA, Wikman G. A randomized trial of two different doses of a SHR-5 Rhodiola rosea extract versus placebo and control of capacity for mental work. *Phytomed* 2003, 10(2-3):95-105.
- 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, 19(2):186-99.

Spasov AA, Mandrikov VB, Mironova IA. The effect of rhodaxon on psycho-physiologic and physical adaptation of students to the academic load. *Exp Clin Pharmaol* 2000b, 63: 76-78

Spasov AA, Wikman GK, Mandrikov VB, Mironova IA, Neumoin VV. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of Rhodiola rosea SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. *Phytomed* 2000a, 7(2):85-9.

Tan CB, Gao M, Xu WR, Yang XY, Zhu XM, Du GH. Protective effects of salidroside on endothelial cell apoptosis induced by cobalt chloride. *Biol Pharm Bull* 2009, 32(8):1359-63.

Tharakan B, Manyam BV. Botanical therapies in chronic fatigue. *Phytother Res* 2006, 20: 91-95.

Tolonen A, Pakonen M, Hohtola A, Jalonen J. Phenylpropanoid glycosides from Rhodiola rosea. *Chem Pharm Bull (Tokyo)* 2003, 51(4):467-70.

van Diermen D, Marston A, Bravo J, Reist M, Carrupt PA, Hostettmann K. Monoamine oxidase inhibition by Rhodiola rosea L. roots. *J Ethnopharmacol* 2009, 122(2):397-401.

Walker TB, Altobelli SA, Caprihan A, Robergs RA. Failure of Rhodiola rosea to alter skeletal muscle phosphate kinetics in trained men. *Metabolism* 2007, 56(8):1111-7.

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

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. *Phytomed* 2009a, 16(2-3):146-55.

Wang Q, Wang J, Sun LJ, Hu LP, Li J, Shao JQ, Lu B, Wang YT, Wu B, Wang GH. Salidroside protects the hypothalamic-pituitary-gonad axis of male rats undergoing negative psychological stress in experimental navigation and intensive exercise. *Zhonghua Nan Ke Xue* 2009, 15(4):331-6.

Wiegant FA, Surinova S, Ytsma E, Langelaar-Makkinje M, Wikman G, Post JA. Plant adaptogens increase lifespan and stress resistance in *C. elegans*. *Biogerontol* 2009, 10(1):27-42.

Wing SL, Askew EW, Luetkemeier MJ, Ryujin DT, Kamimori GH, Grissom CK. Lack of effect of Rhodiola or oxygenated water supplementation on hypoxemia and oxidative stress. *Wilderness Environ Med* 2003, 14(1):9-16.

Wu T, Zhou H, Jin Z, Bi S, Yang X, Yi D, Liu W. Cardioprotection of salidroside from ischemia/reperfusion injury by increasing N-acetylglucosamine linkage to cellular proteins. *Eur J Pharmacol* 2009, 24;613(1-3):93-9.

Wu YL, Piao DM, Han XH, Nan JX. Protective effects of salidroside against acetaminophen-induced toxicity in mice. *Biol Pharm Bull* 2008, 31(8):1523-9.

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* 2009a, 61(10):1375-82.

Yin D, Yao W, Chen S, Hu R, Gao X. Salidroside, the main active compound of Rhodiola plants, inhibits high glucose-induced mesangial cell proliferation. *Planta Med* 2009, 75(11):1191-5.

Yu S, Liu M, Gu X, Ding F. Neuroprotective effects of salidroside in the PC12 cell model exposed to hypoglycemia and serum limitation. *Cell Mol Neurobiol* 2008, 28(8):1067-78.

Yu S, Shen Y, Liu J, Ding F. Involvement of ERK1/2 pathway in neuroprotection by salidroside against hydrogen peroxide-induced apoptotic cell death. *J Mol Neurosci* 2010, 40(3):321-31.

Zhang J, Liu A, Hou R, Zhang J, Jia X, Jiang W, Chen J. Salidroside protects cardiomyocyte against hypoxia-induced death: a HIF-1alpha-activated and VEGF-mediated pathway. Eur J Pharmacol 2009, 607(1-3):6-14.

Zhang L, Yu H, Sun Y, Lin X, Chen B, Tan C, Cao G, Wang Z. Protective effects of salidroside on hydrogen peroxide-induced apoptosis in SH-SY5Y human neuroblastoma cells. Eur J Pharmacol 2007, 564(1-3):18-25.

Zhang L, Yu H, Zhao X, Lin X, Tan C, Cao G, Wang Z. Neuroprotective effects of salidroside against beta-amyloid-induced oxidative stress in SH-SY5Y human neuroblastoma cells. Neurochem Int 2010, 57(5):547-55.

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.

Zhu BW, Sun YM, Yun X, Han S, Piao ML, Murata Y, Tada M. Reduction of noise-stress-induced physiological damage by radices of Astragali and Rhodiola: glycogen, lactic acid and cholesterol contents in liver of the rat. Biosci Biotechnol Biochem 2003, 67(9):1930-6.

Zhu J, Wan X, Zhu Y, Ma X, Zheng Y, Zhang T. Evaluation of salidroside in vitro and in vivo genotoxicity. Drug Chem Toxicol 2010, 33(2):220-6.

Zubeldia JM, Nabi HA, Del Rio MJ, Genovese J. Exploring new applications for Rhodiola rosea: can we improve the quality of life of patients with short-term hypothyroidism induced by hormone withdrawal? J Med Food. 2010 Dec;13(6):1287-92.