REFERENCE SHEET:

Rhodiola *rosea*

Pronunciation

Rhodiola rosea (Roh-dee-oh-lah Roh-zeh-ah)

Summary

The Rhodiola plant consists of over 200 species originating from the Himalayan belt, Tibet, China, and Mongolia. Rhodiola is now cultivated for use in supplements in Europe and North America. It is one of the most commonly used plants in Chinese traditional medicine for healthy aging, endocrine activity, cardiovascular health, nervous and immune system stimulation, mental and physical performance, as an adaptogen to fight stress, depression, and anxiety. The two major constituents used to evaluate the quality of Rhodiola *rosea*-derived compounds are salidroside and tyrosol. While polyphenols make up approximately 40% of its constituents, Rhodiola also contains glycosides, organic acids, essential oils, sugars, fats, alcohols, and proteins.

Main Medical Uses

Evidence supports the use of Rhodiola *rosea* (RR) for treating depression, generalized anxiety disorder, mental and physical fatigue, and stress. RR has been studied for its use in cardiovascular conditions, including chronic stable angina pectoris, ischemic heart disease, and protection against myocardial damage. RR has also been associated with improved performance during endurance exercise, antioxidant status, and cognition.

Proprietary Extracts

Proprietary Extract	Formulation	Safety
SHR-5 Standardized Extract	Ethanolic (70%) extract with drug/extract ratio of 4:1 Standardized to contain 3.07% rosavin and 1.95% salidroside	Up to 1360 mg per day over 12 weeks reported safe
WS® 1375 (Rosalin®)	Ethanolic (60%) extract with drug/extract ratio of 1.5–5:1	200 mg, 2x per day over 8 weeks reported safe* 200 mg, 2x per day over 4 weeks reported safe*

*note: WS® 1375 trial sponsored by Dr. Willmar Schwabe GmbH & Co. KG, or one or more authors were an employee of Dr. Willmar Schwabe GmbH & Co. KG.

Associated Depletions and Interactions

Class of Drug	Pharmaceutical	Effect	Class of Evidence
Angiotensin receptor blockers	Losartan (single dose - unspecified) (CYP3A4, CYP2C9, and CYP2C10 substrate, and P-gp)	↓ CYP2C9 activity by 23% with RR pretreatment	D
	Losartan (5 mg/kg)	↑ AUC of losartan 2-fold with 50mg/kg RR in rabbits	D
Pyrrolidinylpyridines	Nicotine (2 mg/kg, 4x per day)	↓ affective and somatic symptoms of nicotine withdrawal in a dose-dependent (10-20mg/kg) manner	D
Hypoglycemic agents	General	↓ blood glucose in rodents with 200mg/kg per day	F

Dosing and Administration

Condition	Dosing & Administration	Outcome	Class of Evidence	Mechanism of Action
Depression	340-680 mg (as SHR-5 standardized extract) per day for 6 weeks	↓ mild to moderate depression, insomnia, emotional instability, & somatization	B	↑ blood-brain barrier permeability to precursors of DA & 5-HT, neural stem cell proliferation in the hippocampus
	340 mg (as SHR-5 standardized extract) per day for 12 weeks	↑ clinically relevant odds of improvement compared to placebo	B	↓ TNF-α & IL-1ß; IL-6; NE & 5-HT in the prefrontal cortex (50); MAO-A & MAO-B activity Modulation of BDNF/TRKB signalling pathway
Fatigue	576 mg (as SHR-5 standardized extract) per day for 28 days	↓ stress-related cortisol awakening response ↑ concentration	B	↑ protein Hsp70 to increase JNK-1 and DAF-16 pathway activity ↓ stress-related cortisol awakening response and NO
Cognition	500 mg (as a standardized extract containing 5% rosavins) per day for 10 days	↑ psychomotor vigilance & working memory	B	↑ p-GSK-3β; PI3K/AKT signalling; antioxidant enzymes TRX, HO-1, & PRXI; BAX/BCL-2 ratio & reversal of hippocampal neuronal loss; SOD & GSH-Px activities; NE, DA, 5-HT & ACh ↓ p-tau; abnormal processing of APP; caspase 3 activation; sodium-azide-induced damage of mitochondria; neuronal death & behavioral dysfunction mediated by polyQ Modulation of AMPK/SIRT1/FOXO1 signalling; modulation of monoamines & opioid peptides expression to increase the adaptability & activity of the CNS; ACh level & activity in the brain

Condition	Dosing & Administration	Outcome	Class of Evidence	Mechanism of Action
Athletic Performance	Single oral dose of 200 mg (extract containing 3% rosavins & 1% salidroside)	↑ time to exhaustion, VO2peak, VCO2peak & pulmonary ventilation	C	↑ blocking of exercise-induced decrease in GDH-Px and SOD; hepatic glycogen
	Single oral dose of 3.0 mg/kg (unspecified form)	↓ heart rate response to submaximal exercise ↑ endurance exercise performance via decreased perception of effort	C	↓ the exercise-induced increase in serum lactate dehydrogenase, creatine phosphokinase, triglyceride, malondialdehyde, and lactic acid ↓ heart rate
	100 mg (extract) per day for 4 weeks	↑ plasma antioxidant capacity post-exercise ↓ superoxide dismutase activity in erythrocytes post-exercise	C	

For an explanation of the classes of evidence, please see the Rating Scales for Evidence-Based Decision Support.

Pharmacokinetics

An active constituent of RR, salidroside, is absorbed in the intestine via the Sodium-dependent Glucose Transporter (SGLT1) in rats and equivalent plasma concentrations are achieved with 24 mg/kg and 48mg/kg doses. Oral bioavailability of salidroside may vary between doses. It was shown that the bioavailability of 12mg/kg of RR was ~32%, 25mg/kg was ~98%, and 100mg/kg was ~52% for both salidroside and p-tyrosol. After absorption, RR's effects may be induced within one hour, while the half-life is also approximately one hour.

Intravenous administration of salidroside results in increased concentrations in the liver, kidney, and heart tissues. Salidroside's deglycosylated metabolite, p-Tyrosol, was found in the heart, spleen, kidney, liver, and lungs. Salidroside was found only in the liver following oral administration. P-Tyrosol was in most tissues other than the brain and kidney.

An in vitro study demonstrated that RR products display varying degrees of inhibitory potential with CYP3A4, CYP2D6, and CYP1A2. The bioactive constituents rosavin, rosarin, rosin, salidroside, and tyrosol were not deemed to cause this inhibition. In addition to CYP3A4, P-gp has also been shown to be inhibited by RR in vitro.

Urinary excretion of salidroside was 64% of the original dose, whereas 0.19% was excreted as p-Tyrosol. Urinary excretion of salidroside was 23.80% of the original doses, whereas 2.25% was excreted as p-Tyrosol.

Adverse Effects

Reported adverse effects, typically rare and described as mild in nature, may include headaches at doses of 200 mg per day over 4 weeks. Reports of adverse effects are rare between doses of 50 mg to 1500 mg per day, suggesting a wide profile of safety. Other reported mild or moderate adverse effects include dizziness and dry mouth.

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