

Evidence-based Efficacy of Adaptogens in Fatigue, and Molecular Mechanisms Related to Their Stress-Protective Activity

[Alexander Panossian](#)¹, [Georg Wikman](#)

Affiliations

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Abstract

The aim of this review article is to assess the level of scientific evidence presented by clinical trials of adaptogens in fatigue, and to provide a rationale at the molecular level for verified effects. Strong scientific evidence is available for *Rhodiola rosea* SHR-5 extract, which improved attention, cognitive function and mental performance in fatigue and in chronic fatigue syndrome. Good scientific evidence has been documented in trials in which *Schisandra chinensis* and *Eleutherococcus senticosus* increased endurance and mental performance in patients with mild fatigue and weakness. Based on their efficacy in clinical studies, adaptogens can be defined as a pharmacological group of herbal preparations that increase tolerance to mental exhaustion and enhance attention and mental endurance in situations of decreased performance. The beneficial stress-protective effect of adaptogens is related to regulation of homeostasis via several mechanisms of action associated with the hypothalamic-pituitary-adrenal axis and the control of key mediators of stress response such as molecular chaperons (e.g. Hsp70), stress-activated c-Jun N-terminal protein kinase (JNK1), Forkhead Box O transcription factor DAF-16, cortisol and nitric oxide (NO). The key point of action of phytoadaptogens appears to be their up-regulating and stress-mimetic effects on the "stress-sensor" protein Hsp70, which plays an important role in cell survival and apoptosis. Hsp70 inhibits the expression of NO synthase II gene and interacts with glucocorticoid receptors directly and via the JNK pathway, thus affecting the levels of circulating cortisol and NO. Prevention of stress-induced increase in NO, and the associated decrease in ATP production, results in increased performance and endurance. Adaptogen-induced up-regulation of Hsp70 triggers stress-induced JNK-1 and DAF-16-mediated pathways regulating the resistance to stress and resulting in enhanced mental and physical performance and, possibly, increased longevity.

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