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File: ■ Adaptogens
■ Fatigue
■ Stress

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RE: Evidence-based Efficacy of 'Adaptogens' in Fatigue and Proposed Molecular Mechanisms of Activity

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

Fatigue can be sufficiently intense that it interferes with a normal life. Temporary fatigue is a minor illness that goes away relatively rapidly. Chronic fatigue, lasting 6 months or more, is not easily cured with rest and sleep. Many people consume 'adaptogenic' herbs to treat stress-related fatigue. The most current definition of an adaptogen is an herbal preparation that can increase resistance to stress. Adaptogens that have been evaluated in well-conducted clinical trials and give evidence of efficacy are: rhodiola (*Rhodiola rosea*); schisandra (*Schisandra chinensis*); eleuthero (a.k.a. 'Siberian ginseng'; *Eleutherococcus senticosus*); Asian ginseng (*Panax ginseng*); and ADAPT-232® (Swedish Herbal Institute; Goteborg, Sweden) a fixed combination of eleuthero, schisandra, and rhodiola root extract. (However, see the reference following this summary, a review of eleuthero's effects relative to its claimed 'adaptogenic' potential).[1]

Several mechanisms of action have been suggested to explain how adaptogens may help people to adapt—become less sensitive—to a stressor: (1) alter nitric oxide (NO) levels, (2) alter cortisol levels, (3) regulate heat shock proteins, and (4) alter adenosine triphosphate (ATP) levels.

Some studies have shown that adaptogens mediate the stress response by preventing the stress-induced increase in NO. More specifically, in vivo and in vitro, adaptogens inhibit inducible nitric oxide synthase (iNOS, the enzyme that is needed for the production of NO) activity and synthesis.

Other studies have claimed that adaptogens mediate the stress response by altering the formation of cortisol. Cortisol is a stress hormone that is involved in homeostasis, its levels increased during stress. With chronic stress, secretion of cortisol is prolonged and can cause a decrease in muscle mass, hyperglycemia (high blood sugar), and suppress the immune response. Patients with chronic fatigue have a higher cortisol response to stress. Optimal corticosteroid levels are needed for efficient cognitive function—cognitive impairment occurs when corticosteroid levels are increased or decreased. A clinical study of 91 patients with mild to moderate depression treated with 170 or 340 mg 2x/day SHR-5® (rhodiola extract; Swedish Herbal Institute; Goteborg, Sweden) for 6 weeks revealed that the rhodiola-induced inhibition of cortisol (an anti-stress effect) produced not only anti-fatigue and increased attention, but also anti-depressive effects, when compared with placebo.

Also, adaptogens affect the expression of heat shock proteins. Heat shock proteins are molecular 'chaperones' involved in stress-induced cytoprotection and adaptation to repeated exposure to a stressor. For example, heat shock protein 70 prevents stress-induced activation of SAPK/JNK (stress activated protein kinase/c-Jun N-terminal protein kinase), which is an early step in apoptosis (programmed cell death). In vivo studies demonstrate that adaptogens prevent JNK-induced apoptosis activation and increase heat shock proteins. Adaptogens can also upregulate certain heat shock proteins that stimulate the immune system and reverse protein denaturation (inactivation) that occurs during acute inflammation.

Stress also causes a decline in ATP, and studies show that adaptogens induce the synthesis of ATP.

The authors conclude that adaptogens should be regarded as a novel pharmacological category of anti-fatigue drugs. They state that adaptogens can reduce stress-induced impairments and improve stress-related disorders. The authors created numerous schematics of the mechanism of action of adaptogens. The manuscript also contains tables of clinical trials. However, the authors do not detail how they chose the studies included in the tables. They also do not summarize the findings of the clinical trials or draw any substantial conclusions from the tables. The main value of this review article is in the proposed detailed mechanisms of action.

—Heather S. Oliff, PhD.

Reference

[1]Davydov M, Krikorian AD. *Eleutherococcus senticosus* (Rupr.& Maxim.) Maxim.(Araliaceae) as an adaptogen: a closer look. *J Ethnopharm*. 2000;72:345-393.

The American Botanical Council has chosen not to reprint the original article.