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Adaptogens

A Historical Overview and Perspective

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The history of the herbal substances known as adaptogens appears to begin with Order No 4654-p of the People's Commissars Council of the Union of Soviet Socialist Republics, dated March 4, 1943 and concerning research work "with the purpose of finding...tonic substances" for both soldiers and persons working in the Russian defense industry during the Second World War.[1] Both the term "adaptogens" and the concept of these herbal substances as compounds that would increase "the state of non-specific resistance" under conditions of stress were formalized in Russia between 1950 and 1960.[2,3]

As originally defined,[4] an adaptogen was a substance that had to: (1) show some nonspecific effect, such as increasing bodily resistance to physically, chemically, or biologically noxious agents or factors; (2) have a normalizing influence on a pathologic state, independent of the nature of that state; and (3) be innocuous and not disturb body function at a normal level.[4]

Thus defined, adaptogens constitute a new class of metabolic regulators that increase the ability to adapt to and avoid damage by environmental factors. Since 1997, the term "adaptogen" has been used as a functional term by Russian health-regulatory authorities, and in 1998 this term was allowed as a functional claim for certain products by the U.S. Food and Drug Administration. Too often, however, the term "adaptogen" is carelessly used, without sufficient experimental evidence to support the criteria for the formal definition of such a substance.

To date, few of the substances called adaptogens comply fully with the formal definition. Empirically, some plants used in traditional medicine, such as *Eleutherococcus senticosus*, *Rhodiola rosea*, *Schisandra chinensis*, and *Bryonia alba*[4-12] appear to meet the criteria of being adaptogens on the basis of the ability to increase nonspecific resistance to stress. Table 1 (page 3) lists the plants most often described as adaptogens.

Despite major differences between various effects of adaptogens and CNS-active drugs (Table 2),[13] some manuals and handbooks—even in Russia, where adaptogens have been recognized as a distinct group of substances—continue to classify them as a group of CNS stimulants or other drugs.[14]

Among the plants used in traditional medicine, *Schisandra chinensis*, whose berries are shown here, meets the criteria for being an adaptogen.

Recent History of Adaptogens

From 1960 to 1970, after a large number of pharmacologic and clinical studies, three plant species—*E. senticosus*, *R. rosea*, *S. chinensis*, and later, in 1993, *B. alba*—were incorporated into official medical practice in the Union of Soviet Socialist Republics, and were industrially produced as standardized extracts in tablet and liquid forms as adaptogens having stimulating, restorative, and anti-

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stress effects. Because these botanical products were also found to be unusually safe, they continue to be used today in Russia in both self-care and physician-prescribed medical regimens.

In self-care, *E. senticosus*, *R. rosea*, *S. chinensis*, and *B. alba* are used by healthy persons as stimulants or tonics in states of fatigue and stress. They are also used in sports medicine for preventing and treating injuries and other somatic conditions. Another use of these four herbs is in occupational medicine, such as for protection against adverse environmental factors, including exposure to low temperature in polar regions and to high noise levels and mechanical vibration in heavy industrial work; in mining; and in medicine for treating acute hepatic poisoning, ischemia from oxygen deprivation, and for acceleratinge recovery after surgery.

Adaptogens are used as curative agents in treating some neurologic and psychiatric disorders, such as asthenia, neurosis, depression, and alcoholism, and in a number of other conditions, as well as being prescribed as adjuvants to other medicines in diseases such as tuberculosis and in conventional cancer therapy.

The concept of "one drug for one disease" does not apply in the use of adaptogens in actual practice. Indeed, not only does evidence suggest that adaptogens display their greatest efficacy in the form of extracts containing a combination of several active substances from a single plant species, but in Sweden and Denmark the concept of combining different adaptogenic substances has led to the development and use of a fixed-ratio combination of standardized extracts of plants such as ADAPT-232.

Reliability of Studies of Adaptogens

A substantial number and range of uncontrolled as well as placebo controlled, randomized, double-blind clinical studies[15-20] have consistently reported standardized extracts of *E. senticosus*, *R. rosea*, and *S. chinensis* as efficient agents for increasing mental and physical work capacity in situations of fatigue and stress.

In the case of *Panax ginseng* root extract, which is fairly popular in the United States, it should be mentioned that a search of Medline, Biosis, the Cochrane Library database, and several other computerized literature databases revealed[16] 16 studies that met the criteria of being double-blind, randomized, and placebo-controlled studies of this agent. However, none of these trials demonstrated a convincingly significant effect of *P. ginseng* root extract on physical performance, psychomotor performance, cognitive function, immune function, or other specific functions,[21] thereby pointing to a general need for more rigorous study of the efficacy and safety of ginseng.[22]

Constituents of Adaptogenic Extracts

In terms of active ingredients, adaptogenic preparations can be divided into the three groups of: (1) those that contain phenolic compounds such as phenylpropanoids, phenylethane derivatives, and lignans,[23-27] whose structural resemblance to catecholamines could suggest an effect on the sympathoadrenal system and possibly imply an effect in the early stages of the stress response; (2) those that contain tetracyclic triterpenes,[28,29] such as cucurbitacin R diglucoside,[11,30] which structurally resemble the specific corticosteroids that inactivate the stress system to protect against overreaction to stressors[31-35]; and (3) oxylipins—unsaturated trihydroxy or epoxy fatty acids structurally similar to leukotrienes and lipoxines.[36-38]

The first group of adaptogenic extracts named above would include the roots and rhizome of *E. senticosus* and *R. rosea*, as well as extracts of *S. chinensis* fruits. The second group of adaptogenic substances are contained in extracts of *B. alba* and *W. somnifera*. The third group of adaptogenic compounds have been found in *B. alba* and *G. glabra*.

Physiologic Basis for the Action of Adaptogens

There is extensive evidence that single-dose administration of adaptogens activates corticosteroid formation, and that repeated dosage with adaptogens normalizes the levels of stress hormones, such as adrenocorticotropic hormone (ACTH).[7,30,35,39-41] It is known that the blood level of corticosteroids increases as a result of long-term training or adaptation, and that a trained organism responds to stress stimuli with only mildly increased activity of the hypothalamic-pituitary axis (HPA), as opposed to a very pronounced increase in activity seen in untrained states.[42] An example of this may be seen in a recent study in which athletes exposed to stress in the form of acute physical exercise exhibited increased formation of cortisol and NO in their blood and saliva.[43] Chronic physical exercise, such as that of well-trained athletes, increases the basal level of these stress-mediating substances in blood and saliva. But while well-trained athletes no longer respond to an acute physical load with an increase in cortisol or NO, *Schisandra* and *Bryonia* activate the formation of both NO and cortisol in these athletes' plasma and saliva, suggesting that these plants provide adaptation to further heavy physical loading.

In other words, adaptogens apparently increase the ability of the stress system to respond to stress stimuli in a manner that tends to preserve homeostasis, particularly by modulating the biosynthesis of eicosanoids—including prostaglandins E2 and F2, 5-hydroxyeicosatetraenoic acid (5-HETE), 12-HETE, and leukotriene B4. Moreover, adaptogens also appear to regulate the basal level of the arachidonic acid that is these substances' precursor, and to also do this under various stressful conditions, such as immobilization, heavy physical exercise, and radiation injury.[44-50]

Although there is a difference in the mode of action and pharmacologic

activity of different adaptogens,[51,52] it is difficult to relate these in a satisfactory way to the differences in adaptogens' various effects. However, the mechanisms of action of adaptogens[30] are mainly related to effects on the neuroendocrine-immunologic axis that constitutes the stress system.[33,34,53-56] The primary site of action of adaptogens appears to be the HPA, and their secondary sites of action the liver and components of the immune and cardiovascular systems.

The effects of adaptogens become somewhat more clear when it is recalled that stress is a defensive response to external factors, and that it stimulates the formation of endogenous "messenger" substances such as catecholamines, prostaglandins, cytokines, NO, and platelet-activating factor, which in turn activate other factors that may either counteract stress or, conversely, induce or facilitate disease. According to this concept,[30,43] the "stress-executing" or "switch-on" mechanism activates the sympathoadrenal system (SAS) and over the longer term also activates the HPA, together with various regulators of cell and organ function.

Table 1. Plants Described in the Literature as Adaptogens

Plant	Family	Author(s)/ year
Acanthopanax sessiliflorum Rupr. et Maxim.	Araliaceae	Brekhman and Dardimov, 1969
Albizzia julibrissin Durazz.	Fabaceae	Kinjo et al., 1991
Aralia elata (Miq) Seem.	Araliaceae	Hernandez et al., 1988
Aralia manshurica Rupr. et Maxim	Araliaceae	Baranov, 1982
Aralia schmidtii	Araliaceae	Baranov, 1982
Asparagus racemosus	Liliaceae	Rege et al., 1999
Atragene sibirica L.	Ranunculaceae	Shilova et al., 2001
Azadirachta indica (Al, Neem)	Melaceae	Koner et al., 1997
Bergenia crassifolia (Fritsch)	Saxifragaceae	Suslov et al., 2002
Bryonia alba L.*	Cucurbitaceae	Panossian et al., 199
Cicer arietinum L.	Fabiaceae	Singh et al., 1983
Codonopsis pilosula (Franch.)Nannf.	Campanulaceae	Lin, 1991
Cordyceps sinisis (Berk.)	Pyrenomycetales	—
Echinopanax elatum Nakai	Araliaceae	Baranov, 1982
Eleutherococcus senticosus Maxim.*	Araliaceae	Brekhman and Dardimov, 1969
Emblica officinalis (Phyllanthus emblica L.*)*	Euphorbiaceae	Xia et al., 1997; Rege et al., 1999
Eucommia ulmoides Oliver	Eucommiaceae	Oshima et al., 1988
Hoppea dichoroma Willd.	Gentianaceae	Ghosal et al., 1985
Ocimum sanctum L.	Lamiaceae	Bhargava and Singh, 1981
Panax ginseng C.A. Meyer	Araliaceae	Brekhman and Dardimov, 1969
Pfaffia paniculata (Marius)Kuntze	Amarantaceae	De Oliveira, 1986
Rhaponticum carthamoides (Willd).Iljin	Asteraceae	Brekhman and Dardimov, 1969
Rhodiola crenulaya (Hook, f. et Thoms) H.Ohba	Crassulaceae	Wang and Wang, 1992
Rhodiola rosea L.*	Crassulaceae	Saratikov et al., 1968
Scutellaria baicalensis (Georgi).	Lamiaceae	Suslov et al., 2002
Schisandra chinensis (Turcz.) Bail.*	Magnoliaceae	Brekhman, 1980
Sterculia plantanifolia L.	Streculiaceae	Brekhman, 1980
Terminalia chebula	Combretaceae	Rege et al., 1999
Tinospora cordiflora Miers	Menispermaceae	Parel et al., 1978; Rege et al., 1999
Trichopus zeylanicus Gaerten.	Trichopodaceae	Singh et al., 2001
Withania somnifera L.	Solanaceae	Singh et al., 1982

*Well-established adaptogen.

Table 2. Differences Between Stimulants and Adaptogens

	Stimulants	Adaptogens
1. Recovery after exhaustive physical loading	Low	High
2. Energy depletion	Yes	No
3. Performance under stress	Decrease	Increase
4. Survival under stress	Decrease	Increase
5. Quality of arousal	Poor	Good
6. Insomnia	Yes	No
7. Side effects	Yes	No
8. DNA/RNA and protein synthesis	Decrease	Increase

Counteracting this is the "switch-off" system, which protects cells and organ systems, and thus the entire organism, from damaging overreaction. This switch-off system includes antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase; interleukins that downregulate various aspects of the immune response; certain corticosteroids and eicosanoids such as prostaglandin E2; and anti-inflammatory mediators.

Excessive activity of the stress system is associated with increased arousal or anxiety, increased blood pressure, gastrointestinal dysfunction, and suppression of the immune response.[33,34,53] For example, both the SAS and the HPA appear to be chronically activated in melancholic depression, which is characterized both by excitation in the form of anxiety and by a suppression of food intake and sexual activity, leading to anorexia and loss of libido. Chronic activation of the HPA has also been observed in such other conditions as anorexia nervosa, panic disorder, obsessive-compulsive disorder, chronic active alcoholism, alcohol and narcotic withdrawal, excessive exercise, and malnutrition. Conversely, a chronic decrease in the activity of the stress system has been linked to states of suboptimal physical and mental function, such as seasonal depression, the postpartum period, and chronic fatigue/fibromyalgia syndromes.[33,34]

Under the conditions of stress that exist in normal homeostasis, the activities of the stress switch-on and switch-off systems are in dynamic balance. According to this concept, adaptogens can be defined as agents that reduce the reactivity of the host-defense system to various stressors by helping to restore normal homeostasis.[30]

Pharmacologic Assessment of Adaptogens

Tests involving exposure to cold, heat, altered atmospheric pressure and oxygen content, radiation, toxic substances, starvation, fear, and chronic diseases have shown that the most important feature of adaptogens is an ability to increase resistance to both physical and emotional stress. This same property has been suggested by specific biochemical tests, such as of the NO content of blood, saliva, and exhaled air; of blood levels of cortisol, ACTH, and other hormones and other substances; and of such cell functions as phagocytosis and cytokine production both *in vivo* and *in vitro*. It has also been shown that NO donors increase and NO-synthesis inhibitors reduce the duration of swimming of rats carrying a load, reduce the survival of rats and their longevity under hypoxia, and increase immobilization-induced stomach ulcers in rats.[57]

Conclusions and Perspectives of Implementation

The results and findings described above indicate strongly that adaptogens have both specific therapeutic effects in some stress-related diseases and are useful in potentially disease-inducing circumstances. A more definitive demonstration of these qualities awaits further well-controlled clinical trials.

Comparing the concept of "quality of life" with the concept of "adaptogens," it could be suggested that this group of botanicals might be useful in improving quality of life[58] in many categories of patients and healthy subjects. Adaptogens are also likely to have a direct impact on many facets of physical health and psychological health. However, there is so far no clinical evidence for this in terms of quality-of-life and related questionnaire data. The results of such studies will allow the development of evidence-based indications for adaptogens as remedies for improving quality of life. NP

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