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Stress, "A Proxy Killer" and Role of Adaptogen as Antistress Agent

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Abstract

Stress is a non-specific immune response of the body known to alter the physiological homeostasis of the organism resulting in various neuronal endocrinal and visceral functions. Derailment of the immune system contributes for the alteration in the homeostasis and resulting in stress related disturbances. Stress responses are composed of alterations in behavior, autonomic function and the secretion of multiple hormones including adrenocorticotropin hormone (ACTH) and cortisol/corticosterone, adrenal catecholamine, oxytocin, prolactin and renin. The concept of "Adaptogen" as a group of medicinal substances was first adopted by Lazarev. Adaptogens are the substances that push the organism into "a state of non-specific heightened resistance (SNIR)" in order to better resist stressors and adapt to extraordinary challenges. They normalize the body functions; strengthen systems and functions that are compromised by stress and have a protective effect against a wide variety of environmental and emotional stress. Till date various substances (natural, synthetic) and techniques (yoga, exercise) have been used to control the stress and stress related disorder. Among those adaptogens are the substances on which less research has been carried out hence in this article we have made an attempt to review the history, potential and different plausible mode of action of adaptogen along with different experimental animal model for the evaluation of an adaptogen.

Key words:

***Stress, cortisol, homoeostasis, adaptogen, plant extract,* adaptogenic activity.**

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Introduction

Stress has been postulated to be involved in the etiopathogenesis of a variety of disease states, including hypertension, peptic ulcer, diabetes, immuno-suppression, reproductive dysfunctions, and behavioral disorders like anxiety due to involvement of the central nervous system (CNS), endocrine system, and metabolic system [1, 2]. Stress, according to late Dr. Hans Seyle, an early guru on stress, is the non-specific response of the body to any demand made upon it. Stress is the body's physical, mental or chemical reaction when we get excited, confused or we otherwise feel unsafe or threatened. Stress is the outcome of people reacting with one another. If daily demands are easy and well balanced an individual is fine. It is when one decides the pressure is unreasonable or the situation is upsetting, and then the potential for damage occurs [3, 4].

In medical terms, stress is the disruption of homeostasis through physical or psychological stimuli. Stressful stimuli can be mental, physiological, anatomical or physical reaction [5]. When a person experiences stress, the brain responds by initiating 1400 different responses including the dumping of a variety of chemicals to our blood stream. This gives a momentary boost to do whatever needs to be done to survive. If left unchecked, the person can have a heart attack or stroke. Many people start drinking alcohol. They get depressed, find it difficult to sleep, experience chest pain. The body runs out of the immunity to fight diseases. So, very often, these persons die of diseases such as cancer, pneumonia, etc. The stress will never be identified as the cause of the death. Hence we can call stress the 'proxy killer' because some other disease always takes the blame for it [6].

An adaptogenic substance is one that demonstrates a nonspecific enhancement of the body's ability to resist a stressor. Adaptogen claimed to increase nonspecific resistance of an organism to an adverse influence [4].

Ayurveda, the indigenous traditional medical system in India, classifies remedies that prevent disease and counteract aging as *rasayana* or rejuvenation remedies. Plant drugs that promote longevity and antiaging are termed *jivaniya* and *vayahsthapana*

respectively and rejuvenation, *kaya kalp*. Pharmacologic investigations have supported antiaging and memory promoting activities of many of these rasayana remedies. However, not all herbs in the rasayana category fit the adaptogen definition. For example,

Argyreia speciosa contains lysergic acid compounds closely related to LSD. It is often combined with other adaptogenic herbs such as *Withania somnifera* and *Centella asiatica* (Apiaceae) as an aphrodisiac and to deter old age [1, 6].

History of Adaptogens:

In 1943, the People's Commissars Council of the Union of the Soviet Republics charged its scientists with the task of finding tonic substances to strengthen the health of workers in the Russian defense industry during World War II. Thus began the effort to find remedial substances that would increase the protective state of resistance during conditions of stress. N. Lazarev showed that ingestion of certain plant extracts could improve stress markers in laboratory animals, such as cognitive function or oxidative damage. Between 1950 and 1960 these plant remedies were termed adaptogens [7].

Clarification of the term "adaptogen":

The general pharmacodynamic characteristics of an adaptogenic substance were defined by Brekhman and Dardymov as follows:

A) An adaptogen is almost non-toxic to the recipient; B) An adaptogen tends to be non-specific in its pharmacological properties and acts by increasing the resistance of the organism to a broad spectrum of adverse biological, chemical, and physical factors; C) An adaptogen tends to be a regulator having a normalizing effect on the various organ systems of the recipient organism.

The term 'adaptogen' has recently been used as a functional term by some health authorities. In order to avoid confusion, it is necessary to differentiate the term 'adaptogen' from traditional herbal medicinal products of related action: "Tonics" are substances, which mitigate conditions of weakness or lack of tone within the entire organism, or in particular organs. The term is typical for traditional medicine, where tonics are used in conditions of "asthenia". "Stimulants" cause a temporary increase in work-capacity, which is followed by a period of decreased work-capacity. The term is used in modern and in traditional medicine. In contrast to stimulants, adaptogens are reputed to cause an increased work-capacity that is not followed by a decrease [8].

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 adjuvant to other medicines in diseases such as tuberculosis and in conventional cancer therapy [9].

Pharmacological studies in connection with the term adaptogen:

The earliest studies of adaptogens investigated primarily their ability to increase the mental and physical working capacity in humans. After those studies characteristic differences between the effects of adaptogens and those of CNS stimulants became evident. Stimulants that increase the activity of the sympathetic nervous system may produce a sense of euphoria and may be used to increase alertness and the ability to concentrate on mental tasks. Plant adaptogens are reported to stimulate the nervous system by mechanisms that are claimed to be different from those of stimulants, being associated by metabolic regulation of various elements of the stress-system and modulation of stimulus-response coupling. Adaptogens are reputed to have an anti-stress effect mainly towards stresses of a non-infectious agent. In this aspect adaptogens differ from immunostimulants. In addition to their various properties, adaptogens are thought to rebuild strength of the body after stress or fatigue. Clinical trials on adaptogens reported an effective application to persons exposed to high physical and nervous loading, i.e., for athletes. It is reported that muscular activity and nervous loading causes the reaction of stress or stress-reaction that is reduced by usage of adaptogens [8, 9]. The plant adaptogen is defined as "Smooth pro-stressors which reduce reactivity of host defense systems and decrease damaging effects of various stressors due to increased basal level of mediators involved in the stress response". 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 [10]. Theoretically, the ability of adaptogen to increase the nonspecific resistance of animals may be related to its capacity to increase serotonin in the hypothalamus and midbrain. Additional research showed that an intact hypothalamic pituitary adrenal axis and participation of the gonads and thymus were necessary for this anti-stress effect. Furthermore, adaptogen reduces the activation of several components of the stress response system [11].

Constituents of adaptogenic extracts

In terms of active ingredients, adaptogenic preparations can be divided into the three groups:

(A) those that contain phenolic compounds such as phenylpropanoids, phenylethane derivatives, and lignans, 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. They include the roots and rhizome of *E. senticosus* and *R. rosea*, as well as extracts of *S. chinensis* fruits.

(B) those that contain tetracyclic triterpenes, such as cucurbitacin R diglucoside, which structurally resemble the specific corticosteroids that inactivate the stress system to protect against overreaction to stressors. These adaptogenic substances are contained in extracts of *B. alba* and *W. somnifera*.

(C) Oxylipins—unsaturated trihydroxy or epoxy fatty acids structurally similar to leukotrienes and lipoxines. These adaptogenic compounds have been found in *B. alba* and *G. glabra* [12].

Some important adaptogenic herbal formulations

A. Geriforte [24],
B. Siotone [25],
C. Zeetress [26].

Adaptogens increase the overall performance in the following ways:

1. Enhance and sustain energy and endurance, reduce fatigue, Maximize energy transfer.

- Enhance the efficient utilization of glucose and insulin,

- Enhance the efficient utilization of fatty acids: by stimulating the use of fatty acids by the muscle, reduce carbohydrate use, which allows for longer and more efficient exercise.
- Enhance oxygen utilization, by aiding in more efficient cellular ATP transfer and mitochondrial response.

2. Anabolic/anti-catabolic – Help to Gain lean muscle mass, reduce body fat. Shorten recovery and reduce the buildup of toxic waste substances resulting from intense training.

3. Balance endocrine hormones, the Hypothalamus-Pituitary-Adrenal-Axis (HPA), particularly DHEA/cortisol, testosterone, thyroid hormone and human growth hormone; while aiding in the removal of various negative hormones and hormone-metabolites such as estrogen and excess insulin.

4. Improve overall health and well being, giving support to the heart, liver, kidneys, immune and digestive system (athletes often have poor immune systems and reduced levels of glutathione, the body's most important antioxidant).

5. Aid in stress resistance and build stress defense (stress is a major contributor to diminished performance, injury, and a shortened career). Reduce risk of injury, muscle fatigue and cramping [27, 28].

Some important experimental animal models for evaluation of adaptogenic (antistress) activity:

Immobilization stress:

In this model rats are exposed to stress daily for 2 hrs. for a period of 10 days 1 hr. after the drug treatment. Stress is induced by immobilizing the rat with head down, supine position by fixing the animal to a board, inclined at an angle of 60^0. The animals are sacrificed at the end of specified period and blood is collected by cardiac puncture under light ether anesthesia for estimation of serum glucose, cholesterol, triglycerides and BUN. Weight of liver, adrenal gland, spleen and testes are also noted [1].

Swim endurance test:

The mice are treated with the test and standard drugs for 7 days. On the 8^{th} day, the animals are allowed to swim till exhausted in a propylene tank of dimension 37 X 37 X 30 cm, filled with water to a height of 25 cm. The end point is taken when the animal drowned and 'Swimming time' for each animal is noted [10].

Cold restraint stress:

The mice are treated with the test and standard drugs for 7 days. On the 8^{th} day, animals are individually placed in plastic containers of capacity 350 ml. They are immobilized in their normal position, using adhesive tape. The containers are placed in a cold chamber maintained at 4^0 C for 2 hours. The blood is collected by heart-puncture method, in a heparinised tube and WBC count is done using Neubauer's chamber, blood glucose and plasma cortisol level is determined [10].

Swimming induced gastric ulceration:

In this test, a group of animals are treated for a period of 15 days. On the 15^{th} day 1 hr. after treatment all the animals are allowed to swim individually for 5 hrs. After swimming, all animals are sacrificed; stomachs are opened and examined with magnifying lens for degree of ulceration. The ulcerogenic indices are scored [15].

Carbon tetrachloride (CCl_4) induced prolongation of hexobarbital sleeping time in mice: The mice are divided in to two groups of 10 animals each. Control hexobarbital (50 mg/kg, ip) sleeping time is determined by the method of Brodie (1956). After 48 hrs, one group received only CCl_4 orally (0.2 ml/100 g) along with equal quantity of liquid paraffin and other group received extract/drug one hr prior to CCl_4 administration. Hexobarbital is injected half an hour after CCl_4 administration in both the groups and sleeping time is noted [22].

Carbon tetrachloride (CCl_4) induced hepatotoxicity:

In this test CCl_4 is used to produce chemical stress in the form of hepatic damage, this result in structural as well as functional damage of liver. Effect of drug on liver weight, volume and mortality is observed [22].

Gravitational stress:

All animals (rats) are made to in a hang head down position from a horizontal bar daily 2 hrs for a period of 8 days. Immediately after last exposure to stress, all the animals are sacrificed and the blood is collected for estimation of biochemical parameters like serum glucose, cholesterol, triglycerides and blood urea nitrogen (BUN). The weight of organs like liver, spleen and adrenal gland is recorded after washing with alcohol with respect to their body weight i.e. per 100 g b.w. [29].

Heat induced stress:

All animals (rats) are subjected to heat stress by exposing them to a controlled temperature of 40 ± 2^0C daily 1 hr. after the drug treatment for a period of 8 days. Immediately after last exposure to stress, all the animals are sacrificed and the blood is collected for estimation of biochemical parameters like serum glucose, cholesterol, triglycerides and blood urea nitrogen (BUN). The weight of organs like liver, spleen and adrenal gland is recorded after washing with alcohol with respect to their body weight i.e. 100 g b.w. [29].

Carbon clearance test:

This is the simplest model to test phagocytosis. It is the test of phagocytotic efficiency and can be correlated with in vitro granulocyte test. Drug/extract is administered to mice orally or intraperitoneally, after 24 hrs. Each mouse is given an intravenous injection of 0.3 ml of Indian ink dispersion per 30 g b.w. Blood samples from retro-orbital venous plexus are taken at intervals of 3, 6,9,12 and 15 min. The carbon clearance i.e. the rate elimination of carbon from the blood is determined by turbidometric spectroscopy at 650 nm [30].

Noise stress:

Noise is produced by two loudspeakers (15 W), driven by white -noise generator (0 – 26 kHz), and installed 30 cm above the cage. The noise level was set at 100 dB uniformly throughout the cage and monitored by the sound level meter. Each treated animal is exposed for 4 hrs. per day for 15 days. Sheep red blood cells (5 x 10(9) cells/ml) are used to immunize the animals and sacrificed on 16^{th} day. Biochemical indicator of oxidative stress namely lipid peroxidation, antioxidants superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), ascorbic acid in plasma and tissue (spleen and thymus)and corticosterone levels in plasma are estimated. Cell mediated immune response namely foot pad thickness (FPT) Leucocyte migration inhibition (LMI) test are performed only in immunized groups [31].

Social isolation stress:

In this study animals are subjected to social isolation stress for a period of 7-14 days. The animals are

isolated and placed individually in a specially designed isolation cage (45x15x15cm) so that the animals can not see each other. Thus, the social contact of the animal is cut off totally for the stipulated duration of the study. At the end of specified period, the effects of stress on body and organ weights, neutrophil and eosinophil counts, blood sugar, serum cholesterol, and serum transaminase levels are studied [32].

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Conflict of Interests:

Authors have no Conflict of Interest

Table 1: Difference Between Adaptogen And Stimulant [8].

Condition	Adaptogen	Stimulant
Recovery after exhaustive Physical loading	High	Low
Energy depletion	No	Yes
Performance under stress	Increases	Decreases
Survival under stress	Increases	Decreases
Quality of arousal	Good	Poor
Insomnia	No	Yes
Side effects	No	Yes
DNA/RNA and protein Synthesis	Increases	Decreases

Table 2: Some of The Reported Adaptogenic Plants

Name of plant	Part of plant	Family
Trichopus Zeylanicus	Glyco-peptido-lipid fraction	Trichopodaceae [13]
Boerhaavia diffusa	Root powder	Nyctiginaceae [14]
Butea monosperma	Flower	Fabaceae [15]
Evolvulus alsinoides	Whole plant	Convolvulaceae [16]
Bacopa monniera	Whole plant	Scorphulariaceae [17]
Ocimum sanctum	Leaf	Lamiaceae [18]
Pueiraria tuberose	Root	Roxb [19]
Rubia cordifolia	Root	Rubiaceae [20]
Rhodiola rosea	Root	Crassulaceae [21]
Diospyros peregrine	Whole plant	Ebenaceae [22]
Withania somnifera	Root	Solanaceae [23]