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Review article

Plant Adaptogens

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Summary

The term adaptogen has not yet been accepted in medicine. This is probably due to the difficulties in discriminating adaptogenic drugs from immunostimulators, anabolic drugs, nootropic drugs, and tonics. There can be not doubt, however, that, at least in animal experiments, there are plant drugs capable of modulating distinct phases of the adaptation syndrome as defined by Seyle. These drugs either reduce stress reactions in the alarm phase or retard / prevent the exhaustion phase and thus provide a certain degree of protection against long-term stress.

The small number of drugs the antistress activity of which has been proven or reported includes, among others, the plant drugs *Ginseng, Eleutherococcus, Withania, Ocimum, Rhodiola*, and *Codonopsis*. This review summarizes the major findings of pharmacological tests and human studies carried out with these drugs. Currently used assay systems allowing detection of antistress activities are also reported.

At present the most likely candidates responsible for the putative antistress activity of plant drugs are special steroids, phenylprogane compounds and lignanes, respectively. Apart from influencing activities of the pituitary-adrenal axis and inducing stress proteins, many adaptogens also possess immunomodulatory and / or anabolic activities.

Key words: plant adaptogens, general adaptation syndrom, stress, chemistry, antistress assays.

The term adaptogen

This term was coined by the Russian scientist Lazarev in 1947 (Lazarev, 1947) when he discovered the adaptogenic activity of Dibazol (2-Benzyl-benzimidazol) in experiments designed to stimulate non-specific resistance in human subjects.

Lazarev, who called this novel group of pharmacologically active compounds adaptogens, defined them as substances which elicit in an organism a state of non-specifically raised resistance allowing them to counteract stressor signals and to adapt to exceptional strain.

Selye (1937) studied the consequences of stress on the healthy organism. He formulated the General Adaptation Syndrome as a stereotypic non-specific response to stressor signals of variable origins. The adaptation reaction enables the organism to increase its power of resistance against stressors and to adapt to environmental changes. According to Selye (1938b) the factor limiting the adaptabiltiy of an organism is its so-called adaptation energy. This means that the capacity to resist adverse environmental influences is not unlimited but declines with increasing and / or continous exposure to stressor stimulation, and one of the sequelae is faulty adaptation and disease.

Brekhman, who later studied the activities of adaptogenic drugs, delineated the term adaptogen as follows (Brekhman 1980):

1. an adaptogen must show a non-specific activity, i. e. increase in power of resistance against physical, chemical or biological noxious agents
2. an adaptogen must have a normalizing influence independent of the nature of the pathological state;
3. an adaptogen must be innocuous and must not influence normal body functions more than required.

In this sense adaptogens reinforce the non-specific power of resistance against stressors, increase general capacities to

withstand situations of stress, and hence guard against desease caused by overstress of the organism.

Adaptogens and their discrimination from other drugs with related pharmacological activities.

If the term adaptogen in its medical sense is accepted it appears necessary to distinguish adaptogenic compounds from others with related activities. Although it is not possible to draw a firm line there are a number of criteria that allow these other compounds to be classified as immunostimulators, nootropic drugs, anabolic drugs, tonics, and geriatric drugs.

Immunostimulators are compounds that elicit enhanced resistance by stimulating non-specific defense reactions that are more or less antigen-independent (Wagner, 1991) Such compounds cause an increase in non-specific resistance against bacterial, in particular against viral infections, and also against chronic inflammation.

Nootropic drugs, also known as cognition enhancers, are centrally acting psychoactive drugs according to Giurgea (cited in Möller and Horn, 1990) aimed at improving higher brain functions such as memory, learning, perceptive faculty, and the power to think or concentrate. A specific mechanism of action is unknown. It is assumed that nootropic drugs optimize functions of remaining neuronal assemblies (adaptive capacity) and possibly protect them against adverse influences such as impairment of energy and transmitter metabolism (protective capacity). A differentiation between adaptogens and nootropic drugs is difficult as the activity of nootropic drugs is assessed in animal experiments by monitoring biochemical alterations, physiological regulatory systems, and behavior. Hence there is no typical model allowing nootropic activities to be determined but a plethora of different experimental approaches. Recently the German Bundesgesundheitsamt issued a statement "Suggestions for Proof of Efficacy of Nootropic Drugs in Dementia (phase III)", detailing five groups of models to assess their activities (Bundesgesundheitsblatt, 1991).

Anabolic compounds activate anabolic metabolism. They promote the synthesis of nucleic acids, proteins, and hence are general promoters of growth.

Tonics and *geriatric compounds* cannot be defined exactly. They are index terms describing substances that generally incerase performance and thus they are without pharmcological correlates. Tonics have been defined broadly as compounds that ameliorate a lack of tonus and weakness of the entire organism or individual organs. Adaptogens and also all other drugs leading to a general increase in performance could therefore also be described as tonics. Geriatric ompounds are those used in the preventive treatment of age-related diseases or symptoms. For example, stubbornness of elderly subjects may be the external manifestation of a reduced or lacking ability to adapt to novel situations.

The activities of adaptogens against stressors of various kinds is generally regarded to be the most prominent feature of these compounds although immunostimulatory, nootropic, and anabolic effects may also come into play.

Physiological foundations of the mechanism of action of adaptogens.

Definition of stress

Stress can be defined as a state of impaired homeostasis. This state is elicited by various stimuli that are usually referred to as stressor signals. Stressor signals can be due to physical or psychological influences for which the organism is not sufficiently prepared such as injuries, surgery, poisoning, psychological strain etc. They disturb the steady state of an organism which reacts by shifting its equilibrium. This shift is associated with a specific syndrome that has been termed General Adaptation Syndrome by Selye (1936 and 1937).

Selye's Stress Model

Selye (1907–1982) formulated the *General Adaptation Syndrome* as an index term for reactions of an organism in response to stressor signals (Selye, 1936 and 1937). This syndrome manifests itself independently of the nature of the noxious agent. He divided three individual phases derived from experiments with rats:

1. State of alarm

The state of alarm is an immediate response of an organism to stress. Selye observed some responses in rat experiments that occurred stereotypically and were thus independent of the nature of the noxious agent.

In order to rapidly provide energy and drive, the organism enhances sympathetic activities and stimulates the hypothalamus-pituitary-adrenal gland axis. One observes an increase in catecholamin levels and the weight of the adrenals is increased. Selye reported decreases of cholesterol and ascorbic acids in the adrenals which can be explained by the increases production of corticosterone. The weights of thymus, spleens, lymphatic glands, and liver in experimental animals were also decreased as was the body temperature. Fat tissues showed increased catabolism. Acute damage in the digestive tract and the occurrrence of stomach ulcers have been observed. The organism is in a catabolic state and the general stressor-unspecific resistance increased.

2. State of resistance

Repeated or chronic exposure to the stressor signal for several days elicits the second phase of the General Adapta-

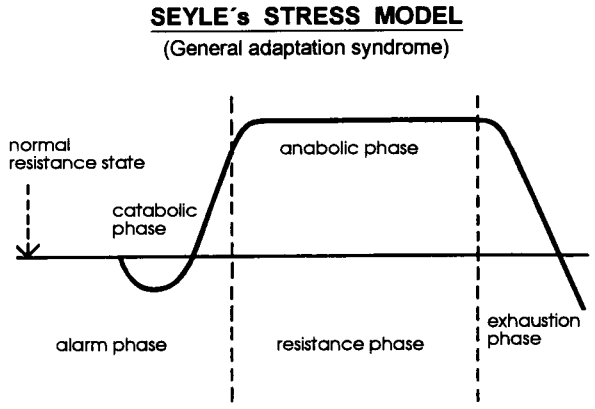


Fig. 1. Specific resistance during the three states of the General Adaptation Syndrome (GAS).

tion Syndrome, the so-called state of resistance. The organism now develops a certain habituation or adaptation, depending upon the nature of the stressor, and thus can withstand the stressor signal. Selye reported a gradual normalization of organ dysfunction observed in rats during the state of alarm. The catabolic state of the alarm phase is gradually replaced by anabolic functions. Stressor-specific resistance replaces the increased non-specific resistance (Fig. 1).

3. State of exhaustion

The power of resistance of an organism against stressors is not inexhaustible. If the strain goes beyond a certain limit or extent the organism enters the state of exhaustion of the General Adaptation Syndrome. Selye observed the same organ damages as those in the alarm phase during the exhaustion period and these led to the death of the animals (Selye, 1936).

In addition Selye's experiments demonstrated that the capacity of an organsim to mount a specific resistance response and to maintain resistance critically depends on factors independent of caloric energy supplies. He named the so-called *adaptation energy* to describe the factor limiting the power of resistance and the duration of resistance. If this energy is exhausted because the stressor signals are either too strong or the duration of stress exposure is too long the state of resistance is either omitted or it is replaced by the state of exhaustion. If the stressor signal is too strong the alarm phase becomes an alarm reaction that usually entails damages so severe that the organism can no longer adapt to it (Selye, 1938 a, b).

Stess proteins as cellular protective mechanisms

Following Selye's initial observations which to a large extent concentrated on organ and endocrine alterations in rat, the influences of stress have also been studied lately at the molecular level. These studies have revealed that prokaryotes as well as eukaryotes possess a number of cellular *stress proteins,* also known as heat shock proteins (hsp), which appear to play a key role in these processes (Santoro, Garaci and Amici, 1990), (Kaufmann, 1991), (Hightower, 1991). The synthesis of heat shock proteins is induced in response to stress, for example in response to elevated temperatures. The structures of stress proteins appear to have been conserved during evolution. According to their molecular masses stress proteins are usually grouped into three different families, hsp90 (= 90 kDa), hsp70 (= 70 kDa), and low molecular mass proteins) (Itoh and Tashima, 1991). Many stress proteins have been shown to play an important role in normal cellular physiology, in particular during periods of development, differentiation, and growth, also under stress-free conditions. Precisely what sort of stimuli induces the expression of stress proteins has not been elucidated entirely. Among other things elevated concentrations of prostaglandins or an accumulation of damaged cellular proteins have been discussed as trigger factors (Santoro, Garaci, and Amici, 1990). It is certain, however, that the rapid induction of the expression of stress proteins under conditions of stress is a vital cellular protective mechanism. Stress proteins can protect cells, for example, by their ability to keep denatured proteins in solution or to renature them, by binding reversibly to steroid receptors, thereby protecting these from binding detrimental ligands, or by their ability to interact with protein kinases. It has been suggested that stress proteins may also influence the immune system and tumor growth (Jäättelä and Wissing, 1992).

The mechanism of action of adaptogens.

The true nature of the mechanism of action of adaptogens has not yet been elucidated to date. There are, however, numerous indications pointing to direct interactions with the general courses of the adaptive process. Most prominent are alterations of endocrine functions of the pituitary adrenal gland axis elicited by pretreatment with adaptogens. Animal experiments have shown that a single administration of an adaptogen raises serum levels of ACTH and corticosterones (Filaretov, Bogdanova, Podvigina, et al. 1988), (Nörr, 1993), (Winterhoff, Gumbinger, Vahlensieck, et al., 1993) whereas a subchronic pretreatment with adaptogens causes a normalization of stress hormone levels and a generally decreased stress predisposition in behavioral tests (Nörr, 1993), (Streuer, Jansen, Winterhoff, et al., 1992). In vivo investigations with rats pretreated with dexamethasone (Filaretov, Bogdanova, Podvigina, et al., 1988) as well as in vitro studies with isolated pituitary primary cultures point to a direct interaction of adaptogens with the pituitary.

It is now known that a plethora of communication links

exist between the endocrine, nervous, and immune systems of an organism, allowing these systems to monitor and control each other's actions. In view of these rather complex reciprocal control mechanisms it can be surmised that systems other than the pituitary adrenegic axis may also be subject to the direct or indirect regulatory influences of adaptogens. For example, many adaptogens have been shown to influence the pituitary gonadal system (Koriech, 1978), (Palmer, Montgomery, Monteiro, et al., 1978), (Siegel, 1979), (Punnonen and Lukola, 1980), (Pearce, Zois, Wynne, et al., 1982), (Barna, 1985), (Winterhoff, Meisel, Vahlensieck, et al., 1993), (Nörr, 1993), to have immunostimulatory actions (Fang, Proksch and Wagner, 1985), Bohn, Nebe and Birr, 1987), (Godhwani, Godhwani and Vyas, 1988), (Mediratta, Dewan, Bhattacharya, et al., 1988), (Liu, 1991b), or to activate cognitive functions (Saito, 1985), (Petkov, Yonkov, Mosharoff, et. al., 1986), (Streuer, Jansen, Winterhoff, et al., 1992), (Zhang and Liu, 1990). To date it is still unknown which cellular mechanisms are addressed during these processes.

Aims of adaptogen treatments

The general aims of adaptogen treatment are a reduction of stress reactions during the alarm phase of the stress response, prevention or at least delay of the state of exhaustion and hence a certain level of protection against long-term stress.

In a similar vein Brekhman has described the long-term effects of adaptogens as a potentiation or prolongation of physiological adaptation (Brekhman, 1980). He reasons that this effect can be attributed to attempts of the organism to protect energy resources from depletion and to accelarate the biosynthesis of proteins and nucleic acids.

Drugs claiming adaptogen efficacy

As the term adaptogen is relatively new it is not found in old treatises on drugs. We present here a retrospective classification of drugs as adaptogens based on empirical medical knowledge criteria and, in some cases, based on experimental data derived from in vitro and in vivo tests. Adaptogenic plant drugs belong to chemically diverse classes of compounds. They differ markedly in their composition. The most important drugs described in the literature are listed in table 1. A selection of these drugs will be discussed in detail in the following paragraphs.

Ginseng

Panax ginseng C. A. Meyer, Araliacae

The tonic activity of ginseng roots was already described in the oldest Chinese pharmacopoeia "Sen-nung Pen ts'ao-ching" dating from the second Han period (Porkert, 1978).

In the light of current knowledge the adaptogenic activity of ginseng can be ascribed to so-called ginsenosides or panaxosides. These compounds are triterpene saponins that differ in the glycosidation grade. With the exception of ginsenoside R_o they are members of the tetracyclic dammaran type (Fig. 2). Ginsenoside R_o has oleanolic acid as an aglycon. The main glycosides are ginsenosides Rb_1 and Rg_1.

Tab. 1. Adaptogenic plant drugs described in the literature.

Plant	Plant Familiy	Plant Part	Literature
Acanthopanax sessiliflorum Rupr. et Maxim.	Araliacea	root	Brekhman and Dardymov, 1969a
Albizzia julibrissin Durazz.	Fabaceae	stem bark	Kinjo, Higuchi, Fukui, et al., 1991
Aralia elata (Miq.) Seem.	Araliaceae	root	Hernandez, Hancke and Wikman, 1988
Aralia manshurica Rupr. et Maxim.	Araliaceae	root	Baranov, 1982
Aralia schmidtii Pojark.	Araliaceae	root	Baranov, 1982
Cicer arietinum L.	Fabaceae	seeds	Singh, Handa, Rao, et al., 1983
Codonoposis pilosula (Franch.) Nannf.	Campanulaceae	root	Liu, 1991a
Echinopanax elatus Nakai	Araliaceae	root	Baranov, 1982
Eleutherococcus senticosus Maxim.	Araliaceae	root	Farnsworth, 1985
Eucommia ulmoides Oliver	Eucommiaceae	stem bark	Oshima, Takata, Hikino, et al., 1988
Hoppea dichotoma Willd.	Gentianaceae	root	Ghosal, Jaiswal, Singh, et al., 1985
Leuzea carthamoides (Willd.) DC.	Asteraceae	root	Brekhman and Dardymov, 1969a
Ocimum sanctum L.	Lamiaceae	leaves, stems	Bhargava and Singh, 1981
Panax ginseng C.A. Meyer	Araliaceae	root	Baranov, 1982
Panax quinquefolium L.	Araliaceae	root	Liu and Xiao, 1992
Rhodiola crenulata (Hook. f. et Thoms.) H. Ohba	Crassulaceae	root, rhizome	Wang and Wang, 1992
Rhodiola rosea L.	Crassulaceae	root, rhizome	Ssaratikov, Krasnov, Chnikina, et al., 1968
Schizandra chinensis (Turcz.) Baill.	Schizandraceae	seeds	Brekhman, 1980
Tinospora cordifolia Miers.	Menispermaceae	stem	Patel, Goyal and Shah, 1978
Trichopus zeylanicus Gaertn.	Dioscoreaceae	leaves	Pushpangadan and Sharman, 1990
Withania somnifera L.	Solanaceae	root, seeds	Singh, Nath, Lada, et al., 1982

Tab. 2. Antistress effects of Panax ginseng root extracts and ginsenoside fractions proved in animal experiments.

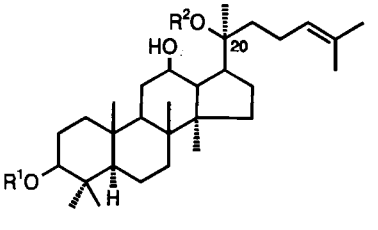
Sample	Animals	Application	Stressor	Literature
aqueous extract	mice	i.p.	emotional stress (open field test)	Bittles, Fulder, Grant, et al., 1979
aqueous extract	mice	p.o.	forced exercise stress, hanging stress	Saito and Bao, 1984
root powder suspended in destilled water	rats	p.o.	emotional stress (open field test, thirsty rat conflict test)	Bhattacharya and Mitra, 1991
ginsenoside fraction	rats	i.p.	cold stress	Bombardelli, Cristoni and Lietti, 1980
ginsenoside fraction	mice	i.p.	radioactivity	Takeda, Katoh and Yonezawa, 1982
ginsenoside fraction	mice/rats	i.p. resp. p.o.	ethanol treatment	Joo, 1984
ginsenoside fraction	mice	i.p.	heat stress	Yuan, Wu and Yang, 1988
ginsenoside fraction	mice	i.p.	hypoxia stress	Qu, Cao and Ma, 1988

Further constituents of ginseng are essential oil, the sesquiterpene β-element, polyacetylenes (Shoji, 1985) (Kim, Kang, and Lee, 1989), salicylic acid, vanillic acid (Han, Han, and Park, 1985), polysaccharides, and ubiquitous amino acids, fatty acids, sterines, and sugars.

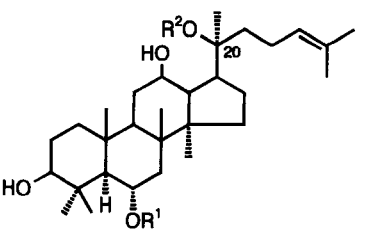
The adaptogenic efficacy of ginseng, i.e. an elevated power of resistance, has been demonstrated in animal experiments with a variety of stressors (Tab. 2).

Endocrinological investigations involving measurements of ACTH and corticosterone serum levels following intraperitoneal administration of ginseng saponin fractions and various pure ginsenosides (Rb_1, Rb_2, Rc, Rd, Re) have shown that all preparations markedly elevate ACTH and corticosterone serum levels (Hiai, Yokoyama, Oura, et al., 1979a, b). Pretreatment with dexamethasone, which blocks hypothalamus and pituitary functions, prevented ginseng saponin-mediated release of ACTH and corticosterone. It can be assumed, therefore, that the liberation of corticosterones after administration of ginseng is not a direct effect but occurs indirectly via release of ACTH from the pituitary. In vitro investigations of steroid receptor binding have shown an affinity of ginseng saponins for gestagen, mineralocorticoid, and, in particular, glucocorticoid receptors (Pearce, Zois, Wynne, et al, 1982). In vitro tests with rat testes demonstrate that the ginseng saponin fraction causes an increase in DNA and protein synthesis (Yamamoto, Kumagai and Yamamura, 1977). Human studies have revealed that in additon to the typical symptoms of elevated corticoid levels (e.g. nervousness, sleeplessness) overdoses of ginseng cause perturbations of functions mediated by sex hormones such as swelling of the breast, amenorrhoea, and increased libido. These symptoms have been designated *Ginseng abuse syndrome* by Siegel (Siegel, 1979).

Increases in physical performance has been demonstrated in animal experiments: in mice ginseng saponin fractions prolong to complete exhaustion the swimming phase in swim tests after intraperitoneal or oral administration (Bombardelli, Cristoni and Lietti, 1980). Brekhman has observed that mice subjected to climbing tests on freely swinging ropes show various graded signs of anti fatigue effects



20 (S)-Protopanaxadiol



20 (S)-Protopanaxatriol

Ginsenoside	R^1	R^2
Rb_1	Glc^2-Glc	Glc^6-Glc
Rb_2	Glc^2-Glc	Glc^6-Ara (p)
Rc	Glc^2-Glc	Glc^6-Ara (f)
Rd	Glc^2-Glc	Glc

Ginsenoside	R^1	R^2
Re	Glc^2-Rha	Glc
Rf	Glc^2-Glc	H
Rg_1	Glc	Glc
Rg_2	Glc^2-Rha	H

Fig. 2. Panax ginseng - Ginsenosides.

Tab. 3. Antistress effects of Eleutherococcus senticosus root extracts and eleutherosides proved in animal experiments.

Sample	Animals	Application	Stressor	Literature
ethanolic extract	rats	p.o.	alloxane treatment	Bezdetko, Brekhman, Dardymov, et al., 1973
ethanolic extract	rats	p.o.	immobilization stress	Brekhman and Kirillov, 1969c
ethanolic extract	mice/rats	i.p.	cytostatica treatment	Goldberg, Shubina and Shternberg, 1971
ethanolic extract	mice/rats	p.o.	cold stress	Abramova, Chernyi, Natalenko, et al. 1972a
ethanolic extract	mice	i.p.	$NaClO_4$treatment	Elkin, 1972
aqueous extract	mice	p.o.	acute stress	Takasugi, Moriguchi, Fuwa, et al., 1985
aqueous extract	mice	p.o.	chronic stress	Nishiyama, Kamegaya, Iwai, et al., 1985
eleutheroside B	rats	i.p.	immobilization stress	Brekhman and Dardymov, 1969b
eleutheroside B	mice	p.o.	acute stress	Takasugi, Moriguchi, Fuwa, et al., 1985
eleutheroside B	mice	p.o.	chronic stress	Nishiyama, Kameagaya, Iwai, et al., 1985
eleutheroside E	rats	i.p.	immobilization stress	Brekhman and Dardymov, 1969b
eleutheroside E	mice	p.o.	acute stress	Takasugi, Moriguchi, Fuwa, et al., 1985
eleutheroside E	mice	p.o.	chronic stress	Nishiyama, Kamegaya, Iwai, et al., 1985

following administration of a variety of ginsenosides. The efficacy of individual ginsenosides was found to be markedly greater than that of total extracts (Brekhman and Dardymov, 1969b)

Peroral administration of an aqueous ginseng extract or of ginsenosides Rb_1 and Rg_2 during passive avoidance response tests with mice have shown a marked improvement in learning capacities negatively influenced by stress. Ginsenoside Rb_1 was shown to be particularly effective. In vitro ginsenoside Rb_1 has been shown to enhance nerve growth factor-mediated outgrowth of neurites from cultures of embryonic brain cortex. In addition this compound effectively protected these cells against colchicine (Saito, 1985).

These results suggest that ginsenosides are the main active ingredients responsible for the activities of Panax ginseng roots. Han, Han and Park (1985) have proposed that phenolic compounds, due to their anti-oxidative activities, be considered as the active adaptogenic sompounds. However, this theory is less compelling as there are many plant derived compounds with anti-oxidative activities that do not possess adaptogenic activities.

Siberian ginseng

Eleutherococcus senticosus Maxim. Araliaceae

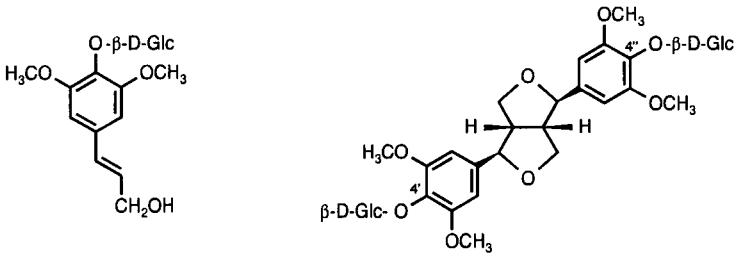
The Siberian ginseng root was discovered in search for a drug that could replace the rather expensive ginseng root. Phytochemical and pharmacological studies of this drug are based on Russian studies mainly on work initiated by Brekhman and his group. The main ingredients of Siberian ginseng markedly differ from those of the ginseng root. They can be classified into the following groups (Farnsworth, 1985), (Bladt, Wagner and Woo, 1990), (Slakanin, Marston, Guedon, et al. 1991), Nörr, 1993):

1. phenylpropane derivatives: syringin = eleutheroside B, sinapin alcohol, coniferyl aldehyde, chlorogenic acid, caffeic acid derivatives
2. lignane derivatives: syringaresinol-4',4",-O-β-D-diglucoside = eleutheroside E (D), syringaresinol-4'-O-β-D-glucoside, syringaresinol, sesamin
3. coumarine derivatives: isofraxidin, isofraxidine-7-O-glucoside etc.
4. polysaccharides
5. further compounds: sterines, oleanolic acid, essential oils, sugars.

The antistress activities of ethanolic extracts of Eleutherococcus senticosus or of compounds derived thereof have been proven in many animal experiments, the most important of which are summarized in Table 3.

Experiments with healthy human subjects in which single doses of 2.0 to 16.0 ml of the extract were given orally have also demonstrated stress-reducing activities without any adverse effects. In sick patients Brekhman has corroborated the normalizing effect required for a classification as an adaptogen. The tolerance of the Eleutherococcus extract was excellent with only a few patients suffering from slight adverse effects such as headaches, increased blood pressure, sleeplessness (Farnsworth, 1985).

Endocrine activities of Eleutherococcus are revealed by increases in the weights of the suprarenal glands; at the same time decreases in cholesterol and ascorbic acid contents suggest an increased synthesis of corticosteroids (Brekhman, 1980). Recent experiments with primary cultures of rat pituitaries have shown a significant liberation of ACTH following addition of aqueous Eleutherococcus extracts at doses of 0.1 mg/ml. Basal levels of luteinizing hormone secretion were also elevated significantly, (Winterhoff, Gumbinger, Vahlensieck, et al., 1993) In vivo experiments with rats reveal that a single intraperitoneal dose of an aqueous extract standardized for eleutheroside B and E at a dose of 3 mg/kg significantly enhances the liberation of cortiocosterone while a subchronic administration of the same extract (i.p. 3 mg/kg or p.o. 500 mg/kg)did not lead to any significant alterations in ACTH or corticosterone levels or of body or organ weights after seven weeks. A remarkable finding in these experiments was the observation that elevations of corticosterone serum levels induced by



Eleutheroside B = Syringin

Eleutheroside E = (-)-Syringaresinol-4',4"-O-β-D-diglucoside

Fig. 3. Eleutherococcus senticosus - Eleutherosides B and E.

mild stress was suppressed significantly in animals treated subchronically, intraperitoneally as well as per os. These animals also were less stress-prone in behavioral test models (Nörr, 1993), (Winterhoff, Gumbinger, Vahlensieck, et al, 1993), (Streuer, Jansen, Winterhoff, et al., 1992). Dardymov has shown that a four week course of high-dose intraperitoneal administration of eleutherococcus (5 ml/kg daily) in immature mice causes an increase in the weights of the seminal vesicles and prostate gland and also increases the RNA contents of the seminal vesicles (Dardymov, 1972a). The anabolic activity of eleutherococcus extracts following intraperitoneal administration in rats was demonstrated by a stimulation of protein synthesis in pancreas, liver, and suprarenal gland (Todorov, Sizova, Kosaganova, et al., 1984). Eleutherococcus compounds have shown affinity to mineralocorticoid and glucocorticoid receptors as well as gestagen and estrogen receptors in vitro (Pearce, Zois, Wynne, et al., 1982). Nikaido and coworkers have shown that eleutheroside E blocks the activity of cAMP phosphodiesterase in vitro and this could explain earlier findings of Brekhman revealing increases in cAMP levels (Nikaido, Ohmoto, Kinoshita, et al., 1981).

Physical performance: In some performance tests with human subjects and also in swim tests with mice extracts of eleutherococcus have been shown to improve physical performance demonstrated previously for other adaptogens (Farnsworth, 1985), (Dardymov, 1971). The animal swim test has shown that eleutherococcus extracts and eleutherosides improve perseverance in mice (Brekhman and Dardymov, 1969a). Administration of eleutherosides (15 mg/kg, 1 day before test begin) retarded inhibition of RNA polymerase activities in muscle and liver caused by swim test-induced stress (Bezdetko, Brekhman, Dardymov, et al., 1973). The improvement in perseverance in rat swim tests after administration of eleutherosides was blocked by inhibitors of protein or nucleic acid synthesis (Dardymov, Bezdetko, and Brekhman, 1972b).

CNS activity: Animal experiments have shown that administration of eleutherococcus extracts (s.c. 0.05–1 mg/kg and i.v. 0.02–2 mg/kg) can cause EEG alterations that may be taken as evidence for stimulatory CNS effects (Marina, 1966). A two-week course of the extract (peroraly, 1 ml]/kg) in rats led to increases in noradrenaline and serotonin in the brain (Abramova, Chernyi, Natalenko. et al., 1972a, b). Peroral application of 500 mg/kg for seven weeks of an aqueous eleutherococcus extract led to improvement in learning and memory abilities in an active avoidance rat model (Streuer, Jansen, Winterhoff, et al., 1992).

Immunomodulation: a double-blind study with 36 human subjects has shown that Eleutherococcus improves non-specific immune reactivities as determined by quantitative flow-cytometry. Immunocompetent cells, in particular T lymphocytes and natural killer cells were found to be markedly increased after administration of the extracts for four weeks (Bohn, Nebe and Birr, 1987). Pure polysaccharides stimulated phagocytosis activity in vitro and in vivo (Fang, Proksch and Wagner, 1985).

At present the question of active principles responsible for these activites cannot be answered. Since eleutherococcus roots do not contain ginsenoside-like compounds it appears that glycosides such as syringin (eleutheroside B) and (-)-syringaresinol-4', 4"-O-β-D-diglucoside (= eleutheroside E) may be mainly responsible for the adaptogenic activity demonstrated already in animal experiments (Fig. 3)

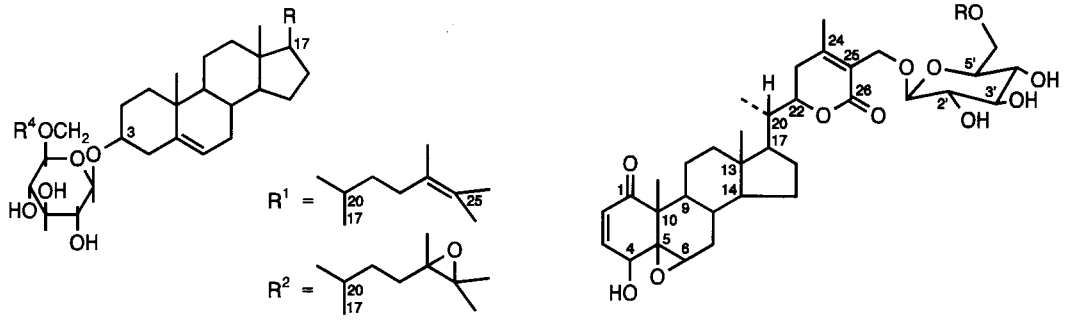
Ashwagandha "Indian ginseng"

Withania somnifera L., Solanaceae

The leaves of this plant are used in Indian folk medicine for the local treatment of skin tumors (Hoppe, 1987). The roots are said to act as tonic and roborans that protect the body against diseases by "maintaining a healthy balance of body powers" (Bhattacharya, Goel, Kaur, et al., 1987).

Apart from several alkaloids the roots contain the steroid lactone Withaferin A and related Withanolides. The sitoindosides IX and X isolated by Ghosal are C-27-glycowithanolides (Ghosal, Bhattacharya, et al., 1989) while the sitoindosides VII and VIII are acylsteryl glucosides (Bhattacharya, Goel, Kaur, et al., 1987) (Fig. 4).

Singh et al., using albino rats, have investigated the anti-



Sitoindoside VII : R = R^1 R^4 = palmitoyl
Sitoindoside VIII: R = R^2 R^4 = palmitoyl

Sitoindoside IX : R = H
Sitoindoside X : R = palmitoyl

Fig. 4. Withania somnifera - Sitoindosides.

stress activities of seed extracts after intraperitoneal administration. These extracts significantly improved protection against stomach ulcers caused by stress or aspirin. Oral administation of the extract (60 mg/kg) for three days mitigated the milk-induced leukocytosis in mice (Singh, Nath, Lata, et al., 1982). The isolated compounds sitoindosides VII and VII and also sitoindosides IX and X protected rats against stress-induced stomach ulcers. Withaferin A showed no activity (Bhattacharya, Goel, Kaur, et al., 1987), Ghosal, Bhattacharya, et al., 1989).

The anabolic activity is demonstrated by the significant increases in body weight observed in albino rats after peroral administration of the extract for one month (Singh, Nath, Lata, et al., 1982).

Measurements of physical perseverance in mice pretreated with Withania extract (i. p.) showed almost a doubling in the endurance time in swim tests (Singh, Nath, Lata, et al., 1982).

Immunomodulation: In contrast to immunostimulating total activities demonstrated for Withania extracts Withaferin A had immunosuppressive effects (Ghosal, Bhattacharya, et al., 1989)

CNS activity: Mice subjected to the Porsolt test, which is characterized by sustained period of behavioral despair after forced swimming stress have shown a markedly shortened period of the immobile state after intraperitoneal administration of sitoindoside VII and VIII. This antidepressive effect may be due to a reduction in stress efficacy or influences on monoamine metabolism in the brain (Bhattacharya, Goel, Kaur, et al., 1987). Other investigations have shown that stress induces a significant increase in Corpus striatum dopamine receptors in rats and that this effect can be suppressed by pretreatment with Withania somnifera or Panax ginseng extracts (Saksena, Singh, Dixit, et al., 1989). Peroral administration of sitoindoside IX and X have demonstrated marked improvements in learning and memory abilities in mice subjected to a step-down test as well as improvements in short-term and long-term memory. Withaferin A was also found to be ineffective in these tests (Ghosalal, Srivatava et al., 1989).

These results seem to suggest that sitoindoside VII, VIII, IX, and X are mainly responsible for the adaptogenic activities in Withania somnifera in spite of their different steroidal structures.

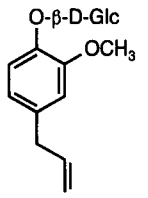
Tulsi, "Holy Basil"

Ocimum sanctum L., Lamiaceae

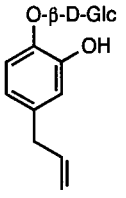
Ocimum sanctumis known in India as Tulsi or holy Basil. This plant is dedicated to Krishna and is cultivated in many temple gardens. Traditional Indian medicine uses this plant for a variety of indications. In addition, extracts prepared from leaves or stems have their proven place as a tonic.

Ocimum sanctum leaves contain a volatile oil of variable composition. Apart from eugenol other main components are methylchavicol, caryophyllen, and methyleugenol (Pareek, Gupta and Maheshwari, 1982), (Knobloch and Herrmann-Wolf, 1985), (Philip and Damodaran, 1985), (Laskar and Majumdar, 1988), (Skaltsa, Tzakou and Loukis, 1988), (Laakso, Seppänen-Laakso, Herrmann-Wolf, et al., 1990).

Leaves also contain the flavon aglycons luteolin and apigenin and their 7-O-glucuronides in additon to C-glycosides orientin and molludistin and the triterpenic acid ursolic acid (Nair, Gunasegaran and Joshi, 1982), sterines, β-carotene, and fatty acids (Skaltsa, Couladi and Phillianos, 1987). Recent phytochemical investigations of the leaves

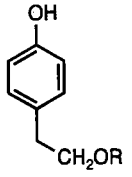


Eugenol-1-O-β-D-glucoside

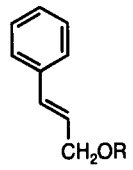


4-Allyl-catechol-1-O-β-D-glucoside

Fig. 5. Ocimum sanctum - Phenylpropane glucosides.



p-Tyrosol: R = H
Salidrosid: R = β-D-Glc



Cinnamon alcohol: R = H
Rosavidin: R = β-D-Glc-α-L-Ara

Fig. 6. Rhodiola rosea - constituents.

have shown the flavonoids vicenin-2, apigenin-7-O-β-glucoside, luteolin-5-O-β-D-glucoside, luteoline-7-O-β-D-glucoside, and cirsilineol as well as derivatives of phenylpropane such as 4-allyl-catechol-1-O-β-D-glucoside and eugenol-O-β-D-glucoside (Fig. 5). Furthermore, oleanolic acid and various plant acids such as rosmarinic acid and aldehydes such as vanillin have been found (Nörr and Wagner, 1992), (Nörr, 1993).

Antistress activity: peroral administration of a 70 % enthanolic extract (200 mg/kg) has been shown to improve resistance against liver damage caused by carbon tetrachloride in mice. Mortality rates were reduced in the treatment group from 50 % to 10 %. Stomach ulcers induced by cold stress, immobilization stress, or treatment with aspirin were significantly less frequent in groups of rats treated with 100 mg/kg (i. p.) one hour before the test. In addition, resistance against experimentally induced leukocytosis was also improved significantly (Bhargava and Singh, 1981).

Physical performance of mice subjected to a swim test was shown to be enhanced after intraperitoneal administration of the extract (i. p. 100 mg/kg, 1 hour before test begin) without altering suprarenal gland weights or their contents in ascorbic acid (Bhargava and Singh, 1981).

Endocrine activity: The ethanolic leaf extract (0.01, 0.01, 1 µg/) has been shown in vitro to lead to significant liberation of ACTH in primary cultures of pituitary cells. Aqueous and n-butanol fractions obtained from these extracts significantly stimulated ACTH release at concentrations of 0.009 and 0.001 µg/ml, respectively (Winterhoff, Gumbinger, Vahlensiek, et al., 1993), (Nörr, 1993).

Oral administration of various Ocimum sanctum extracts has been shown with increasing lipophilic nature of the solvent to induce progressive infertility in female rats (Batta and Santhakumari, 1970).

Immunomodulation: Godwhani et al. have described immunostimulatory effects in albino rats after treatment for 10 day with oral dosis of an aqueous or methanol extract (Godhwani, Godhwani and Vyas, 1987).

CNS activity: Animal experiments have shown activity in the central nervous system of a 70 % ethanolic extract given orally that was comparable to low dose treatment with barbiturates: Seizures were ameliorated and the action of pentobarbital was prolonged. Stimulated activities such as enhanced motor activity were also observed (Sakina, Dandiya, Hamdard, et al., 1990). Shortened periods of immobility were observed in the Porsolt behavioral despair test after oral administration of the extract. These resembled the effects elicited by imipramine, and the effect could be blocked by haloperidol treatment. These observations suggest possible dopaminergic influences (Sakina, Dandiya, Hamdard, et al., 1990).

The investigations described so far have been carried out with total extracts of leaves or stems and leaves. Bioactive components of these extracts are still unknown. It is conspicuous that ethanolic-aqueous extracts of Ocimum sanctum leaves again contain phenylpropane glycosides as main constituents apart from eugenol and flavonoid glucuronides (Nörr, 1993).

Rhodiola rosea

Rhodiola rosea L., Sedum roseum Scop. Crassulaceae

Rhodiola rosea is used by the aborigines of Siberia to prevent fatigue and general disinclination to work (Ssaratikov, Krasnov, Chnikina, et al., 1968).

Apart from salidroside (p-tyrosol glucoside) cinnamon alcohol glycosides are believed to be the major active compounds (Fig. 6). Rosavidin, the cinnamyl-O-(6'-O-L-arabinosyl)-D-glucoside deserves special mention (Ssaratikov, Krasnov, Chnikina, et al., 1968), Thieme, 1969). Further constituents are p-tyrosol (2-(4-hydroxyphenyl)-ethanol) and cinnamon alcohol, volatile oils, anthraglycoside, β-sitosterine, daucosterol, monoterpenes, flavonoids, and 16-18 % tanning agents (Zapesochnaya and Kurkin, 1982, 1983), (Kurkin, Zapesochnaya and Shchavlinskii, 1984a, b, 1985a), (Kurkin et al. 1985b, 1988), (Hoppe, 1987), (Zapesochnaya et al. 1985).

Antistress activity: Increased resistance against brain electrotraumas and other stressors has been observed after

oral administration of Rhodiola rosea extracts, in particular of salidroside and various cinnamylglycosides (Barnaulov, Limarenko, Kurkin, et al., 1986). Salidroside at doses of 2 mg/20 g s. c. increased the period of forced retention time at perpendicular rods until complete exhaustion. Salidroside administration also protected against turpentine oil-induced leukocytosis in animal models. Subcutaneous administration of salidroside prolonged the time of repeated forced holding in albino mice (Ssaratikov, Krasnov, Chnikina, et al., 1968).

Endocrine activity: Rhodiola extract (01, 0. 0,1, 1 µg/ml) singificantly increased ACTH release in primary cultures of rat pituitary cells in vitro (Nörr, 1993). Following injection of adrenaline salidroside showed antihyperglycemic activity while exerting antihypoglycemic effects following administration of insulin (Ssaratikov, Krasnov, Chnikina, et al., 1968).

CNS activity: Stimulatory effects have been observed in animal models following administration of extracts. However, the activity of chloral hydrate and further compounds with inhibitory effects of the central nervous system was not altered (Ssaratikov, Krasnov, Chnikina, et al., 1968). Rats treated with 0, 1 ml of the extract showed improved learning behavior and memory in a maze model 24 hours after treatment. Further treatment for 10 days caused significant improvement of long-term memory. These results, however, could not be corroborated in step-down and shuttle box tests (Petkov, Yonkoff, Mosharoff, et al., 1986). Human studies have shown that doses of 10 mg salidroside after oral administration improved mental abilities. In correction tests the error rates were reduced by approximately 50 % (Ssaratikov, Krasnov, Chnikina, et al., 1968).

So far salidroside and rosavidin have been suggested as the major active compounds. The plant contains a number of other glycosides with similar structures, for example the cinnamyl glucoside rosin. The chemical relationship between these compounds and syringin (= eleutheroside B), isolated from Eleutherococcus senticosus and thought to be one of its bioactive compounds, deserves special mention. Syringin also has a phenylpropane backbone and is glycosidated, albeit at another postion.

Dangshen

Codonopsis pilosula (Franch.) Nannfeldt, Campanulaceae

The root of this plant known as Dangshen in China is used in traditional Chinese medincine as a substitute for the more expensive ginseng root. Dangshen is listed in the Chinese pharmacopoeia and is primarily used as a mild roborans and tonic (Porkert, 1978), (Paulus, 1987), (Stöger, 1991). Codonopsis root, in contrast to ginseng root, does not contain ginsenosides (Wong, Chiang, and Chang, 1983). The main constituents of the root are sterines and triterpenes (Lee and Jung, 1979), Wang, Cai and Zhao, 1982), (Kim and Lee, 1984), (Chen, Wang, Han, et al., 1985), sesquiterpenes (Wang, Xu, Hattori, et al., 1988), (Wang, He, Mao, et al., 1991), the alkaloid perlolyrin (Liu, Liang and Tu, 1988, 1989a, b), various furan, and pyridine derivatives (Wang, Xu, Hattori, et al., 1988), alkanyl and alkenyl glycosides (Mizutani, Yuda, Tanaka, et al., 1988), mono and polysaccharides (Liu and Wang, et al., 1983), (Zhang and Zhang, 1987), amino acids, and inorganic elements (Cai, Wang, Han, et al., 1982) in addition to phenolic compounds and the phenylpropaneglycosides syringin and tangshenoside I (Wang, Xu, Hattori, et al., 1988), (Han, Yang, He, et al., 1990). Recently the polyacetylene compounds tetradeca-4E,12E-diene-8,10-diyne-1,6,7-triol and tetradeca-4E-diene-8, 10-diyne-1,6, 7-triol-6-O-β-D-glucoside and also the phenylpropane coniferyl alcohol and its dimers, pinoresinol and dehydrodiconiferyl alcohol have been isolated from the methanolic extracts of Codonopsis pilosula roots (Nörr, 1993), (Nörr and Wagner, in press).

Antistress activity: The decoction of Codonopsis roots has been shown to prolong the life span of mice after oral administration under conditions of limited oxygen supply by reducing oxygen consumption. The n-butanol fraction of this extract reduced the incidence of drug or stress-induced stomach ulcers (cited in Liu, 1991b).

Endocrine activity: The plasma corticosterone level in mice was increased after administration p. o, i. p., or i. v. of the root extract. Reductions of corticosterone levels after treatment with dexamethasone were reduced after administration of the n-butanol fractions of the extract, suggesting effects at the pituitary or superior central structures (cited in Liu, 1991b). The methanolic root extract caused a marked but not significant secretion of ACTH in primary cultures of rat pituitary cells (Nörr, 1993).

Immunomodulation: The root extract improved non-specific immune defenses by increasing phagocytotic activities (cited in Liu, 1991b).

CNS activity: A 20 % ethanolic root extract improved memory capacities in experimentally compromised mice and rats subjected to a step-down test after oral administration (once daily 30, 45, 60 g/kg) for three days. Intraperitoneal administration of the n-butanol fraction revealed similar effects at lower doses (mice: i. p. 0. 2–0, 6 g/kg; rats: i. p. 0. 15–0. 3 g/kg). Influences on the cholinergic systems were discussed by Zhang and Liu (1990).

Apart from the two polyacetylene compounds the main constituent of the methanolic extract is again a phenylpropane compound, Tangshenoside I (Fig. 7). With respect to the possible bioactive compound in this extract it is again the close structural relationship of this compound and Syringin, discussed as the bioactive compound in Eleutherococcus, that is the most prominent feature. Although Syringin was found in Codonopsis (Wang, Yu, Hattori, et al., 1988), its concentration appears to be too low to discuss any significant participation in the pharmacological activi-

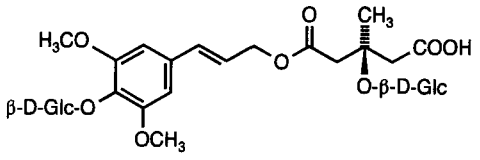
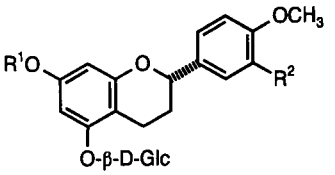


Fig. 7. Codonopsis - Tangshenoside I.



Dichotosin:	$R^1 = CH_3$	$R^2 = H$
Dichotosinin:	$R^1 = CH_3$	$R^2 = OCH_3$
Diffutin:	$R^1 = H$	$R^2 = OCH_3$

Fig. 8. Hoppea dichotoma - Flavan glycosides.

ties of the extract. The adaptogenic activities of the polyacetylene compounds have not been investigated so far.

Hoppea dichotoma

Hoppea dichotoma Woild. Gentianaceae

Hoppea dichotoma is used in Ayurvedic medicine in the treatment of hemorrhoids and hydropsy and as a nerve tonic. Adaptgenic constituents have been isolated from root extracts of this plant. They have been identified as the flavane glucosides Dichotosin, Dichotosinin, And Diffutin (Fig. 8) (Ghosal, Jaiswal, Singh, et al., 1985).

The anti-stress activity of these compounds after intraperitoneal administration in albino rats has been shown, for example, by improved performance in swim tests and an improved protection against stress-induced stomach ulcers. The corticosterone levels in serum was elevated 1.5-fold in unstressed rats. When glycosids were administered in combination with the corresponding aglycons the anti-stress efficacy was markedly increased and this was interpreted as synergistic effects (Ghosal, Jaiswal, Singh, et al., 1985).

Previous studies designed to prove scientifically the bioactivities of adaptogens

Anti-stress activity tests

As adaptogens are expected to cause non-specific resistance against any kinds of stressors, experimental animals (rat, mice) are usually pretreated with the putative adaptogen and then exposed to stressor stimuli. Alterations in general resistance against stressors observed in these animals are compared with control groups.

Enhanced power of resistance can manifest itself by a variety of phenomena, including:

- prolonged maintenance of body temperature following temperature stress (cold stress)
- improvement in coordinate functions
- improved cognitive abilities
- increases in locomotor and explorative activities
- improvement in emotional behavior
- prevention of stomach ulcers induced by aspirin, cold stress, or immobilization
- decreases in milk-induced leukocytosis
- improvement in resistance against various toxic compounds
- improvement of general immune defences.

The relationship between stress and the resulting pituitary release of ACTH or adrenergic corticoid production has been known for a long time and is schematically depticted in Fig. 9.

It has been stated already that these mechanisms play a key role in the efficacy of adaptogens although the exact relationships have not been fully elucidated.

Raised levels of ACTH and corticosterones observed after administration of test drugs are usually taken as endocrinological evidence for the adaptogenic activities of the test drug. At the same time measurements of ACTH and corticosterone levels in stress models can be valuable parameters allowing evaluation and monitoring of the stress disposition of animals, in particular if combined with stress behavioral studies (Nörr, 1993), (Winterhoff, Gumbinger, Vahlensieck, et al., 1993), (Streuer, Jansen, Winterhoff, et al., 1992).

Tests measuring altered physical performance

Improvement of physical performance appears to be caused by a more economical use of energy resources although the exact mechanisms have not been elucidated so far. The energy sources in muscle tissues are ATP, creatine phosphate, and glycogen. Brekhman et al. (Brekhman and Dardymov, 1971) have been able to show that a decline in the levels of these energy sources during a two-hour swim test with rats was reduced by intraperitoneal administration of the eleutheroside total fraction.

Alterations in physical performance are usually measured by the so-called swim test: Following administration of the

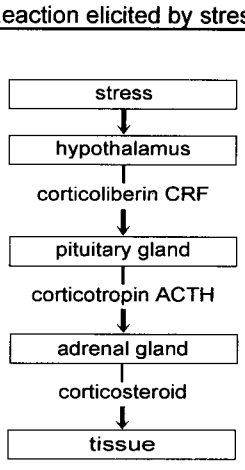


Fig. 9. Stress and the hypothalamus pituitary adrenal axis.

putative adaptogen mice are forced to swim in porcelain tanks filled with water of 26–30° C until they are completely exhausted. Improved performance is usually assayed as a prolonged time period spent in the swim test as compared to an untreated control group.

Another test employs the ability of animals to climb and stay on an endless rope. In this test the animals are placed in a closed box containing an endless perpendicular moving rope (conveyor belt effect.). They are forced to climb and to stay on the rope by applying a slight electrical current to the bottom of the box. The physical strength is exhausted when the animals remain on the bottom of the box.

Anabolic efficacy tests

Anabolic activities appear to be linked to anti-stress activities of adaptogens. Again the causes remain to be elucidated. Anabolic effects may be a response of the endocrine system to alterations of glucocorticoid levels caused by increased levels of the growth hormone somatotropine (STH). A possible stimulation of STH secretion by dopamine and dopamine agonists may also be important (see also: results obtained in Porsolt tests). On the other hand a general interference with activities of the pituitary-gonadal axis may also play a role.

An anabolic activity of adaptogens in animal models is indicated by increases in body weight and accelerated growth of young animals. In additon, direct stimulatory effects on DNA, RNA or protein synthesis have been described (Yamamoto, Kumagai and Yamamura, 1977), (Todorov, Sizova, Kosaganova, et al., 1984).

Tests mesauring alterations in brain metabolism

The reasons for improved mental ability following administration fo adaptogens have not been elucidated so far. Influences of adaptogens on learning and memory abilities are usually tested in models established previously to test nootropic activities. Currently used models include, in particular, active avoidance response tests and passive avoidance response tests such as the step-down test.

In the step-down test mice are placed on a platform that itself is surrounded by a low voltage electrically charged metal grid. If the animals step down from the platform and enter the grid they receive a slight elctric shock. Mice with improved learning and memory abilities will recognize more easily and more rapidly the platform as a pain-free zone than untreated rats. In addition, several maze models are utilized in which rats are conditioned by food to find the right path.

Porsolt (Porsolt, Anton, Blavet, et al., 1978) has developed the behavioral despair test, also known as forced swimming test to evaluate the efficacy of antidepressive drugs. Due to the close connections between stress and the development of depressions (behavioral despair) this test is also used to evaluate the efficacy of putative adaptotgenic drugs.

If a mouse is forced to swim on a small glass cylinder freely floating in water it will desperately try initially to escape or to swim. The mouse then subsides and becomes immobile with only a few minimal movements of the limbs to keep the head over the water level. After a total period of 20 minutes spent in the test situation the animal is removed and caged. The test is repeated 24 hours later. The total test now lasts only 5 minutes. After entering the immobile state, the duration of immobility is measured. Administration of antidepressive drugs or dopamine agonists (e.g. bromocriptine) prolongs the time before the onset of the immobile state and thus shortens this immobile phase during the test period of five minutes. Drugs blocking dopamine receptors such as haloperidol do not elicit such effects.

The results obtained with some tested adaptogens (Sakina, Dandiya, Hamdard, et al., 1990) have shown a markedly shortened duration of the immobile phase and appear to suggest dopaminergic activities, in particular, because the effects could be blocked by pretreatment with haloperidol.

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