

Drugs with Adaptogenic Effects for Strengthening the powers of resistance

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Translator's Summary

Adaptogens, first defined in the 1950s by Lazarev are substances that normalize body functions, strengthen systems and functions compromised by stress and have a protective effect against a wide variety of environmental and emotional stress. In this article, German researchers define the term and identify ways in which science can identify medicinal plants that have these abilities. A number of plant adaptogens are reviewed, including ginseng, eleuthero, and the Japanese Kampo medicine, Shosaikoto.

What is meant by Adaptogens?

The concept "Adaptogen" was coined in 1947 by the Russian scientist, Lazarev (1). He discovered the adaptogenic effect of dibasol (2-benzylbenzimidazol) in tests aimed at the stimulation of non-specific powers of resistance in test subjects. Lazarev, who called this new group of medically-effective substances, "adaptogens," defines them as substances meant to put the organism into a state of non-specific heightened resistance in order to better resist stresses and adapt to extraordinary challenges.

It was Selye who examined the actions and consequences of such stresses on the healthy organism (2). He formulated the "General Adaptive Syndrome" (GAS). As a consistent, non-specific response of the organism to stressful influences of totally diverse types, the adaptive reaction enables the body to heighten its power of resistance towards stresses, and to adapt to external conditions. The limiting factor within this adaptive capacity is, according to Selye, determined by the so-called "Adaptations Energy" (3) of the organism. This means that the resistance reserves towards unfavorable influences are not inexhaustible, but they diminish by extreme stressfulness. The consequences are misadaptation and diseases.

Brekhman, who examined the effects of adaptogenic drugs at a later point, summarized the concept "adaptogen" in 1958, as follows (4):

1. It must show a non-specific effect (raising the power of resistance to toxins of a physical, chemical or biological nature).
2. It is to normalize, independent of the type of pathological condition.
3. It must be harmless and disturb the body functions as little as possible. Accordingly, adaptogens are to strengthen the non-specific powers of resistance to non-infectious stresses, raise the general performance capacity during stress situations and thereby prevent diseases that could develop due to over-stressing the organism.

Adaptogens and their Definition and Differentiation from other Drugs with Related Pharmacological Effects

If one accepts the concept of adaptogenic effects in the medical sense, it is necessary to define and differentiate them from other remedies of related action. Although a strict differentiation is not possible, there is a number of criteria which allow a formal arrangement of these other drugs in immune stimulants, Nootropics, anabolics, tonics and geriatric aids. Immune Stimulants are substances which bring about a heightened resistance through the stimulation of non-specific defensive processes which are largely

independent of antigens (5). There occurs a rise in non-specific resistance towards bacterial, and especially viral infections, as also in chronic inflammation. Nootropics (cognition enhancers), according to Giurgea (cited in ref. 6) are effective psychopharmacological agents which are said to improve the higher integrative brain functions, such as memory, learning, understanding, thinking and the capacity for concentration. No specific mechanism is known. It is assumed that nootropics stimulate existing neural synapses to optimum performance (adaptive capacity), and also for damaging influences, such as disturbances of the energy and neurotransmitter metabolism or ischemia (protective capacity).

A delineation of adaptogens from nootropics is difficult simply because the analysis of the effective action of nootropics is undertaken with animal experiments, whereby biochemical changes, physiological regulatory systems and types of behavior are registered. Thus it applies also to nootropics that there exists no typical model for the analysis of their effects, but only a broad palette of diverse experimental approaches. Recently, in an announcement of the BGA, "recommendations for establishing effectiveness of nootropics in the indications area of dementia (phase III) are given, whereby 5 groups of models are quoted for analysis of activity (7).

Anabolics are substances which activate the anabolic metabolism. They promote the synthesis of nucleic acids and protein metabolism; thereby in general, growth. No precise conceptual definition can be given for tonics and geriatric remedies. They fall into the category of wellness enhancers and are therefore without pharmacological significance.

Tonics, according to a very generalized definition, are substances which mitigate conditions of weakness or lack of tone within the entire organism, or in particular organs. Being adaptogenic, like all the others, generally, adaptogens raise one's capacity, therefore may also be included in the group of "tonics."

Geriatric remedies are substances serving as a preventative treatment of "old-age diseases." "Stiffness and age-conditioned rigidity, are possibly the outer manifestations of diminished or lacking ability to adapt.

It is seen as characteristic of adaptogens that their anti-stress effect towards stresses of a non-infectious variety, always stands in the foreground. Although in so-called adaptogens, "immune-stimulating, nootropic, or metabolic effects have also been observed.

Physiological Foundations of the Adaptogenic Effect; Goals of Adaptogenic Application Selye (2,8) placed the reactions of the body to affecting stresses under the (wellness enhancing) concept of general Adaptations Syndromes (GAS). This syndrome, which manifests independent of the damaging agent, has been divided into three phases by Selye, based on rat experiments (Fig. 1)

1. The "Alarm Reaction"

The first phase of the GAS, observed in rats, normally 6 to 48 hours after the initial effect of a damaging agent, leads to changes which are always of the same nature, and independent of the type of stressor, comparable to shock symptoms.

The activity of the sympathetic nervous system is heightened, catecholamine levels are raised. On the basis of the increased corticosteroid production the content of cholesterol and ascorbic acid, in the adrenals, is diminished. The weight of the adrenal gland increases, the weight of the thymus, spleen, lymph glands and liver diminish. Body temperature is lowered_ there occurs acute damage in the digestive tract, with the frequent

formation of stomach ulcers. Through the condition of the catabolic metabolism, the organism is in a degenerative phase, and the non-specific stress resistance capacity is raised.

2. The "Stage of Resistance"

If the stressor continues to act on the organism, there follows the second phase of AAS after a few days. The organism now responds with heightened capacity of resistance to the damaging factors. The changes observed during the alarm phase normalize themselves gradually and anabolic functions prevail. The organism is becoming increasingly resistant towards the damaging agent. The optimal adaptation has been reached.

This adaptation is strictly stressor-specific. The heightened stressor non-specific power of resistance observed during the alarm phase is no longer observable.

3. The Stage of Exhaustion"

If the impact of a stressor goes beyond a certain limit, the third phase of AAS is reached: The resistance of the organism is exhausted. The "energy of adaptation," according to Selye (3) is used up. The condition of adaptation reached in phase 2 is lost. In animal experiments, death usually occurs at this stage. The damage in organs correspond to those occurring during the alarm phase (8).

In human beings, the exhaustion phase leads to the development of diseases such as stomach ulcers.

Insert Figure 1: Rise and fall of resistance during the three phases of the General Adaptation Syndrome, according to Selye (11).

Besides the general adaptation syndrome of Selye, the "stress proteins" or "heat-shock proteins," which have been proved in Prokaryotes and Eukaryotes need to be pointed out in this connection (9,10). The syntheses of these proteins is induced during a stressful event, such as heightened temperature. Many of the "stress proteins" play an important role for normal cellular function under stress-free conditions, especially in periods of development, differentiation and growth. Which types of stressors in particular lead to the induction of "stress proteins," is to this day still quite unclear. Heightened prostaglandin concentrations or an accumulation of damaged cell proteins are, for example, discussed as possible trigger factors for "stress proteins." It is certain that the prompt induction of "stress proteins" in stressful situations is a vitally-necessary protective function for the cell. "Stress proteins" can for instance, protect sensitive cell proteins from irreversible denaturalization, influence RNA- and protein-synthesis in a specific way, temporarily inactivate certain receptors or initiate immune reactions.

The general hope regarding adaptogens is the reduction of stress-reactions in the alarm phase, the delay or avoidance of the exhaustion stage, thereby providing a certain protection towards stress. In a similar way, Brekhman (4) describes the adaptogenic effect as a strengthening or extending of the physiological adaptation. He bases this effect on the attempt of the body to protect energy resources from depletion and to accelerate the biosynthesis of proteins and nucleic acids.

Drugs Known for Adaptogenic Effects

Because the concept of the "adaptogenic effect" is of relatively recent occurrence, one cannot find it in old drug lists. The assignment into the group of adaptogens happens, therefore retrospectively, on the basis of xx criteria, based on experiential medical data and in a few cases, on data gained from *in vitro* and *in vivo* tests. Adaptogenic drugs are

found in the most diverse families they are distinctly different in the pattern of their constituents. Table 1 lists drugs described in the literature as having adaptogenic effects.
Ginseng

Panax ginseng C.A. Meyer, Araliaceae

The tonifying effect of the ginseng root has been described in a Chinese text as early as the 1st century after Christ. According to current understanding, the adaptogenic effect of the drug is ascribed to the ginsenosides or panaxosides. We are dealing here with diversely glycosolized triterpene saponins which, with the exception of ginsenoside R0, belong to the tetracyclic dammarane-type. Ginsenoside R0 has oleanolic acid as the aglycone. The chief glycones are the ginsenosides Rb1 and Rg1 (Fig. 2).

Insert Table 1: Drugs to which adaptogenic effects are ascribed.

Additional constituents previously cited include essential oil, the sesquiterpene beta-elemene, polyacetylenes (12,13), salicylic- and vanillic-acid (14), polysaccharides, as well as ubiquitously-occurring amino acids, fatty acids, sterines and sugar.

In animal experiments, heightened powers of resistance from diverse stresses through an adaptogenic effect is noted (Table II):

Beyond these, pharmacological examinations using ginseng extracts, ginseng fractions and ginsenosides have revealed, besides adaptogenic effects, anabolic and nootropic properties.

In endocrinological examination for testing ACTH and corticosteroid profiles after i.p. application of ginseng saponin fractions, as well as diverse purified ginsenosides (Rb1, Rb2, Rc, Rd, Re), all applications have led to a distinct rise in ACTH and corticosteroids (19). After pre-medication with Dexamethasone, which has a blocking effect on the hypothalamus and the pituitary gland?, the release of ACTH and corticosteroids through ginseng saponins, did not occur.

Consequently, the site of activity of the saponins seems to be on the pituitary or the hypothalamus and not on the adrenals. Accordingly, the secretion of the corticosteroids after an application of ginseng seems to be not directly caused, but indirectly via the release of ACTH by the pituitary gland.

In vitro studies on the binding of steroid receptors showed a ginseng saponin affinity toward gestational, mineralcorticoid and especially glucocorticoid receptors (20). In vitro examinations with rat testes showed that a ginseng saponin fraction affected a rise in DNA- and protein-synthesis (21). In the animal model, an increase of physical capabilities has been proven (17, 22):

In the swimming test, ginseng saponin fractions, given to mice either i.p. or p.o., led to a postponement of exhaustion (17). Brekhman (22) performed tests with mice in which he registered, after an application of diverse ginsenosides, in a "climbing test on a moving rope," an antifatigue effect by stages. In these, the effect of the single ginsenoside was far superior to that of the total extract.

The oral intake of a watery ginseng extract, as well as the ginsenosides Rb1 and Rg2 by mice, during a pre-treatment phase, clearly affected an improvement of the learning behavior that had been influenced by negative stress (passive avoidance response model). Ginsenoside Rb1 proved to be especially effective. In vitro, ginsenoside Rb1 potentized the stimulating effect of the "nerve-growth factor" on the production of nerve fibers in the embryonal cerebral cortex. Moreover, it gave protection against cellular toxins, such as colchicine (18).

Insert Table II: Heightened powers of resistance proven in animal experiments after administration *Panax ginseng*.

Insert Fig. 2: *Panax ginseng*- Ginsenosides- constituents of Ginseng root

The results seem to confirm that ginsenosides are the responsible chief constituents of the *Panax ginseng* root for causing these effects. The theory put forth by Han (14)_namely that it is principally the "antioxidant effects" of phenolic compounds which brings about the adaptogenic reaction_ is less convincing because there are many other plant substances with "antioxidant" effects; such as for example, flavonoids, vitamin C, etc. These substances have not been officially ascribed an adaptogenic effect.

Taiga root, Siberian Ginseng root

Eleutherococcus senticosus Maxim., Araliaceae

In search of a drug which could replace the expensive ginseng root, one came across the Taiga root, originating from Siberia. Its phytochemical and pharmacological processing goes back to Russian works, in particular, that of Brekhman and his circle. The chief constituents are considerably different than those of the ginseng root (Fig. 3). They may be arranged in the following groups (23).

1. Phenyl propane compounds: syringin = eleutheroside B, sinapin alcohol, coniferyl aldehyde, chlorogenic acid, caffeic acid derivatives.
2. Lignanes: syringaresinol-4-4'-0-beta-D-diglucoiside = Eleutheroside E (D), syringaresinol monoglucoiside, syringaresinol, sesamin.
3. Coumarins: e.g. Isofraxidin-7-0-glucoiside and its aglycon, isofraxidin.
4. Polysaccharides.
5. Additional constituents, such as sterins, oleanolic acid, essential oil, sugar.

The anti-stress effect of *Eleutherococcus* extracts have been demonstrated in animal experiments, through a raised protection from the typical organic changes during the alarm phase, as described by Seleye (24).

Improved resistance occurred in diverse models, with regard to a series of stressors (Table 3).

In experiments with healthy probands, stress-mitigative effects have been proven by giving single doses from 2.0 up to 16.0 ml of the extract (p.o.). No side-effects have been observed (29). The required normalizing effect for adaptogens(Brekhmann) has been confirmed (29) in diseased patients. The tolerance of the *Eleutherococcus* extract was very good. Only a few patients complained of side-effects of a mild nature, such as headaches, raised blood-pressure, sleeplessness.

Insert Fig 3: Constituents of the roots of *Eleutherococcus senticosus*

Insert Table 3: In animal experiments, the raised capacity for resistance after administration of *Eleutherococcus senticosus*, was proven.

Eleutheroside B stimulates *in vitro* the activity of the yeast-hexokinase. The inhibition of hexokinase by beta-lipoprotein or by the beta-lipoprotein-corticoid-complex, which is formed in the blood during stressful situations, has been neutralized by eleutheroside B (30).

Endocrine effects of *Eleutherococcus* can be read from an increase in the weight of the adrenal cortex, while the simultaneous decrease in the content of cholesterol and ascorbic acid indicates an increased formation of corticosteroids (4). In recently-performed

examinations, a rise in corticosterone-serum values after the application of intra-peritoneal application of *Eleutherococcus* extracts on rats has been proven (31). After the i.p. application of Eleutheroside B and E, the weights of the testicle and the prostate gland of young mice was raised, the RNA-content of the testicles was simultaneously increased. A corresponding testosterone-like effect has been observed after castration, whereby the deterioration of the testicles and prostate has been avoided by *Eleutherococcus* intake (32). Active constituents *Eleutherococcus*, similar to constituents of ginseng, bind with receptors of gestation-, mineralcorticoid- and glucocorticoid- receptors; but beyond these, also with estrogen receptors (20). The reduction of the c-AMP-phosphodiesterase through eleutheroside E (33), which was already proven in vitro by Nikaido and collaborators, may be the explanation for the rise in the c-AMP-panel already found by Brekhman.

In some performance tests on humans, as also in swimming tests with mice, the improvement in the capacity of physical performance described for adaptogens has been confirmed also for *Eleutherococcus* (29, 34). The improved endurance of rats in the swimming test after application of Eleutheroside has been cut short by giving proteic- or nucleic- acid synthesis blockers (35).

The anabolic effect of *Eleutherococcus* extracts has been proven, after an i.p. application in rats, as a stimulant of protein synthesis in the pancreas, liver and adrenal cortex (36). Also in frog embryos, an anabolic effect has been proven, which was neutralized by puromycin (37). The injection of *Eleutherococcus* extract led to improved circulation in the brain of anesthetized cats (38), and a rise in the content of biogenetic amines in the CNS of rats, (39).

Insert Fig. 4: Sitoindosides, constituents of *Withania somnifera*

Eleutherococcus improves the non-specific immune defense, as has been proven in a double-blind study with 36 probands, through quantitative (Durchflusszytometrie). Immune-competent cells, particularly T-lymphocytes and natural killer cells, were increased after intake for 4 weeks (40). Purified prepared polysaccharides stimulated the phagocytic activity in vitro and in vivo (41).

The question as to the active compounds responsible for these effects is yet to be determined. Because the *Eleutherococcus* root has no compounds which are comparable to ginsenosides, either as yet unknown compounds or the phenylpropane glycoside syringin (= eleutheroside B) and syringaresinol-4-4'-O-beta-D-diglucoside (= eleutheroside E), which have already been used in animal experiments, are to be accepted as responsible.

Ashwaganda, Indian ginseng

Withania somnifera L., Solanaceae

The leaves of this plant are used in India as a folk medicine for a local treatment for skin tumors (42). The root drug is considered a tonic and roborant. It is said to "protect the organism from illness through maintaining the healthy balance of the physical energies (43). The root contains the steroid lactone withaferin A and related withanolides, beside various alkaloids. The sitoindosides IX and X isolated by Ghosal et al. represent C-27-glycowithanolides (44), the sitoindosides VII and VIII, acylesterylglucosides (43) (fig. 4). By examinations of the anti-stress effect, Singh et al. (45) found in albino rats, that extracts of the seeds of *Withania somnifera*, when given i.p., significantly improved the protection against stomach ulcers that were induced by aspirin or stress (45). Oral intake

over 3 days of this extract (60 mg/kg) effected a weakening of the milk-induced leucocytosis in mice (45). Similar anti-stress effects were shown by the sitoindosides VII and VIII: the induction of stomach ulcers through stress was hindered by a pre-treatment with sitoindoside VII or VIII (43). The Porsolt-test, in which mice fall into behavioral despair through forced swimming stress, showed a distinct shortening of the duration of immobility, after giving sitoindoside VII and VIII (i.p.). This anti-depressive effect can come about through a diminishment of the stress effect, or through intervention in the monoamine metabolism of the brain (43). Examinations showed that stress effects in rats led to a significant increase of the dopamine receptors in the *Corpus striatum* and that this effect can be suppressed through pre-treatment with *Withania somnifera* or with *Panax ginseng* extracts (46). The sitoindosides IX and X protected rats after oral application from stress-induced stomach ulcers (44). Withaferin A showed no effects. In contrast to the immuno-stimulating total effect of *Withania* extracts, withaferin A has an immune-suppressive effect (44).

The testing of the physical endurance of mice, after pre-treatment with withania-extract (i.p.) showed a near-doubling of the length of perseverance in the swimming test (45). The significantly increased body weight in albino rats, after one month of extra intake, speaks for the anabolic effect (45).

In learning and memory patterns in mice, sitoindosides IX and X, given p.o. effected a significant improvement in the "step-down test", both in short range and long-range memory. Here, too, the withaferin A showed no effects (44). The results indicate that sitoindosides VII, VIII, IX, and X represent the adaptogenic-active substances of *Withania somnifera*, in spite of diverse steroidal structures.

Tulsi, Holy Basil

Ocimum sanctum L., Lamiacea

Ocimum sanctum is a plant that is known in India as Tulsi, and "Holy Basil." It has gained a solid place as a tonic in traditional Indian medicine (fig. 5). *Ocimum sanctum* leaves contain an essential oil of varying compositions. The chief components are eugenol, methylchavicol, alpha- and beta-bisabolol (47). Additional constituents are the flavonoglyca luteolin and apigenin and their 7-O-glucuronides as well as the C-glycosides orientin and molludistin and the triterpene acid ursolic acid (48).

After p.o. application of the 70% ethanolic extract of the drug, in animal tests, non-specific resistance from stomach ulcers and carbon tetrachloride poisoning was improved (49).

The physical endurance of mice, after i.p. application of the extract, was strengthened, without any increase in the weight of the adrenal gland, and without a lowering of the ascorbic acid-content of the adrenal glands (49).

The CNS-effect of the 70% ethanolic extract (p.o.) in animal tests, was comparable with the effect of low-dose barbiturate rates (50): cramps were mitigated, the pentobarbital-effect was lengthened. However, stimulating effects also showed up in the form of increased motor activity (50).

In the "Porsolt-test" (behavioral despair) (50) the oral intake of the extract led to a shortening of the immobile condition, and thereby to an imipramin(e)-like effect, which could be blocked by giving haloperidol. This behavior allows one to assume an eventual dopamine-like effect.

Godhwani and collaborator (51) describe immune-stimulating effects in albino rats after p.o. intake for 10 days for the watery and methanol extracts. Because the examinations at hand have been made with the total extract from the herb or leaves, no statement can be made about the inherent active constituents. The constituents described until now (see fig. 5) occur as plant components in many drugs, so that their participation in the described adaptogenic effect has little likelihood.

Goldroot

Rhodiola rosea L., Crassulaceae

Rhodiola rosea is used by the ancient Siberians for the prevention of tiredness and reduced interest in work (52). Besides salidroside, the tyrosol-glucoside, cinnamol alcohol glycosides are considered to be the active constituents. Especially notable is the rosavadin, the cinnamyl-0-(6'-0-L-arabinopyranosyl-D-glucopyranosid) (fig. 6). Additional constituents are tyrosol and cinnamic alcohol, essential oil, anthraglycosides, beta-sitosterin, daucosterol, monoterpenes, flavonoids and 16-18% tannins (53, 54). Adaptogenic properties were observed in several tests (52): salidroside-application protected, in the animal model, from an experimental leucocytosis created by turpentine oil (52). After adrenaline injection, the substance showed an antihyperglycemic effect, and after insulin application an antihypoglycaemic effect (52).

In human studies, doses of 10 mg of salidroside (p.o.), led to improved mental capacities: in the "corrections test?", the error rate fell nearly 50% (52). The alcoholic total extract goldroot raised the learning and memory capacity of rats in the "irrgartenmodell-" (maze-model), with a dose of 0.1 ml/animal. Salidroside raised the physical capacities, or the working capacity, in white mice: the subcutaneous application of the substance lengthened the time of "multiply-forced clinging" by white mice (52).

Until now, especially salidroside and rosavadin have been presented as the inherent active constituents, however, the plant contains additional glycosides of similar structure (for instance the cinnamylglucoside rosin). The chemical relationship of the compounds to syringin (=eleutheroside B), which has been isolated from the *Eleutherococcus senticosus* root which also showed adaptogenic effects, is interesting. This substance also has a phenylpropane structure and is glycosylated, although, in another place.

Chickpeas

Cicer arietinum L., Fabaceae

In India, the chickpea is an important food. It is considered especially nutritious because of its high content of proteins, carbohydrate, fat and minerals. The strengthening and "performance elevating" effects seem, however, to go beyond those of a mere food. In the search for the responsible active substance, Singh and collaborators found pangamic acid (fig. 7), also called vitamin B15 (56).

Pangamic acid does indeed show endurance-raising effects in the mouse swimming test (57), however, besides *Cicer arietinum*, corn, soybean, peach kernels and peanuts also contain pangamic acid in comparable concentrations, without these foods having ever been described as adaptogenic.

Hoppea dichotoma Wild.

Gentianaceae

Hoppea dichotoma is used in Ayurvedic medicine for the treatment of hemorrhoids, dropsy, and as a nerve tonic. Constituents acting adaptogenically have been isolated from

a root extract of the plant, and have been identified as the flavan glycosides dichotosin, dichotosinin and diffutin (58) (fig. 8).

The adaptogenic effect of these compounds (i.p. Appl. in white rats) showed, for instance, in raised endurance during the swim test and improved protection towards stress-induced ulcers in the stomach (58). Their corticosteroid profile in the serum had been raised in unstressed rats by 1.5 (58). When the glycosides were given in combination with the relevant aglyca, the anti-stress effect was noticeably raised, which has been interpreted as a synergistic effect (58).

The drugs *Leuzea carthamoides* [Willd.] DC. (root), *Trichopus zeylanicus* Gaertn. (leaves) and *Codonopsis pilosula* [Franch.] Nannf. (root) also seem to have anti-stress effects.

For *Leuzea*, predominantly anabolic effects have been measured, which apparently are caused by the phytoecdysones which they contain. *Trichopus zeylanicus* has been described by Pushpangadan as a potent adaptogen (59). No phytochemical analysis has been performed. *Codonopsis pilosula* "Dangshen", is used in traditional medicine, either by itself, or in diverse combination preparations. In phytochemical examinations, besides other constituents, phenyl propane compounds, such as syringin have been found (60).

Shosaikoto

Shosaikoto is a drug mixture that is used in Japan as a water-extract in Kampo medicine, and is primarily known for its liver-protective and antiinflammatory effects. For the composition of Shosaikoto, see Table IV.

For testing its adaptogenic effectiveness, mice have been put into stress through immobilization (forced fixation) (61): the lowering of body temperature caused by this stress, did not occur after peroral Shosaikoto as also after Diazepam. Also, the diminished motor activity caused by stress, has been mildly improved by both preparations. The hypertrophy of the adrenals, induced by stress, however, was influenced neither by Shosaikoto or Diazepam to any significant degree (61).

An immune suppression caused by stress, was mildly improved by the extract p.o. (61). this could either be based on the immunomodulatory activity (62) or an anti-stress effect. Age-conditioned reduced learning capacity was significantly improved in "passive avoidance response" models of 110-weeks-old rats, after peroral Shosaikoto application. In comparison to the control group, the brains of the treated animals showed raised dopamine and lowered noradrenalin and 4-hydroxy-3-methoxymandelic acid (63). Because we are dealing in Shosaikoto, with a combination of seven diverse drugs, the total adaptogenic effect cannot be assigned to any single drug.

Bupleurum falcatum root (Saiko), the chief component in Shosaikoto, contains triterpene alcohols, the so-called Sakogenins, and their glycosides, the Saikosaponins. The watery drug extract (extracted hot) showed in vitro a c-AMP-phosphodiesterase-blocking effect of about 40% (64). In the animal model, Saikosaponins A and D caused an increase in the plasma concentration in ACTH and cortisol, while Saikosaponin c remained without effect (65).

The influence of *Panax ginseng* and *Glycyrrhiza glabra* on the glucocorticoid metabolism is already known (19, 66).

Although there are numerous phytochemical works relevant to the four other drugs, one cannot ascribe an adaptogenic effect to any of the isolated constituents.

Examinations up until now on the scientific method of proof of the biological activity of Adaptogens

Testing the Antistress Activity

Because an adaptogen is meant to raise the non-specific resistance toward every kind of stress, one exposes animals (mice, rats) after pre-treatment with the assumed adaptogen to diverse stresses and measures the changes in resistance towards toxins, on the basis of a control group.

Any raised capacity for resistance may manifest as an

- * increased capacity for the maintenance of body temperature during the stress of exposure to cold
- * Improvement in the coordinative capacity
- * Improvement in the cognitive faculties
- * Rise in locomotor and explorative activity
- * Improvement in emotional behavior
- * Avoidance of the formation of stomach ulcers after aspirin, stress due to cold or immobilization
- * Lowering of the milk-induced leukocytosis
- * Improvement of resistance toward diverse toxins
- * increase in general immune defense

The connection between stress and the its resulting ACTH and corticosteroid output has long been known and it is reflected in the chain of reaction represented in Table 9.

This mechanism seems to be a key function for the action of adaptogens.

In animal experiments, a stressed rat will have

clearly raised glucocorticoid blood levels. If one treats the animal with an effective adaptogen, nearly normal corticosteroid values are measured after the application of stress. Consequently, the cholesterol and the ascorbic acid values of the adrenal cortex are not lowered and the weight of the adrenal cortex remains nearly constant. After a single application of adaptogens, the ACTH and corticosterin values in the blood rise in non-stressed rats, and after several days of application, the hormone panels appear unchanged. The capacity for adaptation is raised, even with a single application, but it becomes optimal only with use over several days (67). Filaretov and collaborators show in the animal model, that a blockage of the pituitary-adrenal cortex axis leads to a total loss of the adaptive capacity of the organism, and the anti-stress activity of adaptogens fails to occur (67). In endocrinological tests, a rise of ACTH and corticosteroid panels, after the administration of a preparation to unstressed rats, is taken to be an indication of adaptogenic effectiveness.

Testing the Changed Physical Labor Performance Capacity

The improvement of physical performance capacity seems to be based on a more economical use of energy, although the reasons for this phenomenon have not been researched until now. ATP, creatin phosphate and glycogen deliver energy to the muscles. Table IV: Summary of the Ingredients in Shosaikoto

Plant Family Part Used Amount (g)

Bupleurum falcatum L. Umbelliferae root 7.0

Pinellia ternata Breitenbauch Araceae tuber 5.0

Zingiber officinale Roscoe Zingiberaceae rhizome 1.0

Scutellaria baicalensis Georgi Labiatae root 3.0

Zizyphus vulgaris Lam. Rhamnaceae fruit 3.0

Panax ginseng C.A. Meyer Araliaceae root 3.0

Glycyrrhiza glabra L. Leguminosae root 2.0

Brekhman et al. (68) were able to show that the decrease in these energy supplies during a rat swim test of two hours can be reduced through the i.p. application of an eleutheroside total extract.

For measuring changed physical endurance, the so-called swim test is usually undertaken: after giving adaptogens, one makes mice swim in a porcelain tank filled with water at the temperature of 26-30 deg. C. until they are exhausted. The increased performance is measured in the form of increased endurance, compared to a control group.

Another endurance test is the "climbing the endless rope test:" A mouse in an enclosed case must climb a constantly moving (from above to below) endless rope (like a conveyer belt effect), in order to escape the bottom of the chest, which is under a mild electric charge. The physical energy is exhausted when the mouse remains sitting on the bottom.

Testing the Anabolic Effectiveness

Along with the anti-stress effect of adaptogens, there seems to be also an anabolic effect. The actual cause for this remains to be clarified. The anabolic effect could be a response by the endocrine system to the influence of the glucocorticoid level and it may come about through increased releases of growth hormone GH. The stimulation of GH secretion by dopamine and dopamine agonists (see the results of the Porsolt-test) needs to be pointed out (69). In the animal model, the increase in body weight and the acceleration of growth of younger animals point to the anabolic effect of the adaptogens. Beyond that, directly stimulating effects on DNA, RNA or protein synthesis has been observed.

Testing of Changes of Brain Metabolism

The reasons for improved mental capacity after adaptogen intake have not yet been researched. The influence on learning and memory performance can be measured with the "passive-avoidance response" test. One typical test of this type is the "step-down" test (44): Mice are placed on the platform, which is located on top of a metal grid with a weak electric current. If the mouse leaves the platform, it experiences a "light" foot shock by stepping on the grid. A mouse with improved learning and memory capacity will more quickly recognize the platform as a pain-free zone, than the untreated mouse.

Porsolt (70) has developed the "behavioral despair" test, also called "forced swimming" test for the testing of anti-depressives. Due to the close connection between stress and the development of depression (behavioral despair), the test also serves for the testing of adaptogenic efficacy. After the administration of adaptogens, the influence on the monoamine metabolism in the brain can be demonstrated (43,50).

If one puts a mouse into a small glass cylinder (about 12 cm), forcing it to swim in water, it makes desperate attempts to flee or swim in the beginning, but then falls into an immobile condition, in which it makes but minimal motions to keep its head above water. After 20 minutes the mouse is taken out and placed into its usual cage. The test is repeated in 24 hours. This time, the mouse falls much faster into the immobile condition. The length of the immobile phase is measured and the total duration of the test is only 5 minutes. The application of anti-depressives as well as dopamine agonists (e.g. bromocriptin) leads to a delay of the beginning of the immobile phase, and consequently,

to a shortening of the immobile phase during the testing period of 5 minutes. Dopamine receptor-blocking substances (e.g. haloperidol) do not show such effects.

The results of the tested adaptogens could be anticipated by a distinct shortening of the immobile phase to cause a possible dopaminergic effect, particularly because the effect has been canceled through pre-treatment with haloperidol.

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