Effect of adaptogens on the central nervous system

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Abstract

It has been found empirically that some plants, such as *Eleutherococcus senticosus, Rhodiola rosea, Schizandra chinensis* and *Bryonia alba* etc, used in traditional medicine to increase stamina and general well-being, also increase the state of non-specific resistance in stress. These plants have been named adaptogens and are defined as metabolic regulators that reduce the damaging effects of various stressors by virtue of a reduction of the reactivity of the host defence system. Adaptogens increase the ability of the organism to cope with stress, thus implying a curative effect on stress-induced disorders. Such drugs are often classified as preparations which stimulate the central nervous system (CNS) in manuals and handbooks on pharmacology. However, adaptogens differ in significant ways from classical CNS-stimulants. Experiments on frogs show that adaptogens do not have direct anti-narcotic effects on the CNS unlike other stimulants such as phenamine, caffeine etc. The mechanisms of action of adaptogens are related to the regulation of the stress system – neuroendocrine – immune complex, and are associated with the biochemical adaptation of cells and organisms to stress.

A large number of uncontrolled as well as placebo-controlled, randomised, double-blind clinical studies have shown that standardised extracts of *E. senticosus, R. rosea* and *S. chinensis* are efficient at increasing mental and physical work capacity in situations of fatigue and stress, as well as in the treatment of some psychiatric disorders such as neurosis, psychogenic depression, astheno-depressive states, alcoholism etc. Comparing the concept of quality of life with the concept of adaptogens, it is suggested that that this group of botanicals could be useful in improving the quality of life in many categories of patients and even in healthy subjects.

Key words: stress – adaptation – central nervous system – work capacity – fatigue – psychiatric disorders – adaptogens – *Schizandra chinensis – Rhodiola rosea.*

Introduction

During the period 1950 – 1960, the idea of increasing the working capacity and stamina of an individual through the use of extracts of plants used in traditional medicine was developed in the USSR, and the concept of "adaptogens" was introduced to describe materials which could increase "the state of non-specific resistance" in stress (Lazarev 1946, 1962). According to the original definition (Brekhman and Dardymov 1968), adaptogens must: (i) show a non-specific activity, i.e. an increase in level of resistance against physically, chemically or biologically noxious agents; (ii) have a normalising influence independent of the nature of the pathological state; and (iii) be innocuous and must not influence the

normal body functions more than necessary. Later on this definition was updated and adaptogens were defined as a new class of metabolic regulators which increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors (Panossian et. al. 1999).

Since 1997 the term adaptogen has been used as a functional term by the health regulatory authorities in Russia (appendix to order number 202 of July 14, 1997 of the Ministry of Health of The Russian Federation, point # 9. PP 42-2900-9) and, since 1998, also in the USA (FDA, Notice of proposed rule marketing, Federal Register of April 29, 1998).

Table 1 lists the plants most frequently described as adaptogens. Too often, however, the term adaptogen has been carelessly employed in the absence of sufficient experimental evidence in support of the criteria demanded by the formal definition, and few of the agents referred to as adaptogens comply fully with the formal definition. However, extracts of *Eleutherococcus senticosus, Rhodiola rosea, Schizandra chinensis* and *Bryonia alba* (Brekhman 1957; Brekhman and Dardymov 1968; Lebedev 1971; Saratikov 1973; Dardymov 1976; Lupandin and Lapajev 1981; Panossian et. al. 1997) appear to meet the criteria on the basis of their abilities to increase non-specific resistance to stress involving a significant general or universal protective effect concerning the whole organism and its main organ and functions: this latter point relates to the most important feature of adaptogens**.** After a large number of pharmacological and clinical studies had been carried out on these medicinal plants, they have been incorporated into the official medicine in USSR. Adaptogens are now being produced industrially based on these plant extracts (e.g. rodakson tablets from *R. rosea*, and loshtak tablets from *B. alba*) and they show stimulating, restorative as well as anti-stress activities. In manuals and handbooks on pharmacology (Mashkovskij 2000), adaptogens are presently grouped together with psychotropic drugs which act as stimulants of the central nervous system (CNS) despite there being clear differences between adaptogens and other stimulants of the CNS as indicated in Table 2 (Fulder 1980).

Table 1. Plants described in the literature as "adaptogens" (well-established adaptogens are marked *)

Name of plant	Family
Acanthopanax sessiliflorum Rupr. et Maxim.	Araliaceae
Albizzia julibrissin Durazz.	Fabaceae
Aralia elata (Miq) Seem.	Araliaceae
Aralia manshurica Rupr. et Maxim.	Araliaceae
Aralia schmidtii	Araliaceae
Asparagus racemosus	Liliaceae
Atragene sibirica L.	Ranunculaceae
Azadirachta indica (Al, Neem)	Melaceae
Bergenia crassifolia (Fritsch)	Saxifragaceae
Bryonia alba L.*	Cucurbitaceae
Cicer arietinum L.	Fabiaceae
Codonopsis pilosula (Franch.) Nannf.	Campanulaceae
Cordyceppt sinisis (Berk.)	Pyrenomycetales
Echinopanax elatum Nakai	Araliaceae
Eleutherococcus senticosus Maxim.*	Araliaceae
Emblica officinalis, (*Phyllanthus emblica* L.)	Euphorbiaceae
Eucommia ulmoides Oliver	Eucommiaceae
Hoppea dichoroma Wild.	Gentianaceae
Ocimum sanctum L.	Lamiaceae
Panax ginseng C.A. Meyer	Araliaceae
Pfaffia paniculata (Marius) Kuntze	Amarantaceae
Rhaponticum carthamoides (Willd.) Iljin.	Asteraceae
Rhodiola crenulaya (Hook, f. et Thoms) H. Ohba	Crassulaceae
Rhodiola rosea L.*	Crassulaceae
Scutellaria baicalensis (Georgi).	Lamiaceae
Schizandra chinensis (Turcz.) Bail.*	Magnoliaceae
Sterculia plantanifolia L.	Streculiaceae
Terminalia chebula	*Combretaceae*
Tinospora cordiflora Miers	Menispermaceae
Trichopus zeylanicus Gaerten.	Trichopodaceae
Withania somnifera L.	Solanaceae

Table 2. The differences between CNS stimulants and adaptogens.

	Stimulants	Adaptogens
1. Recovery process after exhaustive physical load	Low	High
2. Energy depletion	Yes	No
3. Performance in stress	Decreased	Increased
4. Survival in stress	Decreased	Increased
5. Quality of arousal	Bad	Good
6. Insomnia	Yes	No
7. Side effects	Yes	No
8. DNA/RNA and protein synthesis	Decreased	Increased

As adaptogen drugs have been found to be unusually safe, they may be used both in self-care situations and in medical treatments as prescribed by physicians. As self-care remedies they can be used (in single or repeated doses) by healthy individuals as a stimulant or tonic in fatigue, or after somatic infections or diseases. They may be advantageous: (i) in sports medicine to promote quicker recovery after hard exercise or to reduce damage from over-training; (ii) in occupational medicine to protect against harmful environmental factors such as exposure to low temperatures (in polar regions), to high noise levels or to mechanical vibration (in heavy industry or in mining); and (iii) in acute medicine in cases of poisoning (especially with respect to liver poisons) or ischemia (through reduction of tissue damage from oxygen deprivation), and also as restoratives to speed up recovery after surgery.

The paradigm 'one drug for one disease' is not appropriate for adaptogens since they have many indications and can be used in the treatment of many stress-induced disorders such as asthenia, psychiatric disorders (neurosis, psychogenic depression, astheno-depressive states, alcoholism), certain cardiovascular disorders, ischemia (stroke, heart attack), impaired visual functions of the eye, acute gastrointestinal diseases, liver poisoning, non-insulin dependent diabetes II, rheumatic heart disorders, and even the common cold. As adjuvants to other medicines, adaptogens may be prescribed to enhance curative effects in chronic conditions such as chronic pneumonia, chronic tuberculosis, vascular dystonia, cancer (through reduction of metastasis), and to relieve the debilitating effects of radiotherapy and chemotherapy.

In healthy individuals, adaptogens may also improve stamina and tolerance to infections. A large number and a wide range of clinical studies (both uncontrolled and controlled) have been carried out in Russia, and the results consistently demonstrate the capacity of adaptogen preparations efficiently to increase mental and physical work capacity against a background of fatigue and stress. However, relatively few of the studies reported to date have been placebo-controlled, randomised and double-blind (Engels and Wirth 1997; Darbinyan et. al. 2000; Spasov et. al. 2000a,b).

The active ingredients of adaptogen preparations can be divided into two groups, namely, phenolic compounds and tetracyclic triterpenoids. The phenolic constituents, such us phenylpropanoids, phenylethane derivatives and lignans (Kochetkov et. al. 1962; Kurkin and Zapesochnaya 1986; Norr 1993; Wagner et. al. 1994; Wagner 1995), are structurally related to the catecholamines which are important mediators of the sympathoadrenal system (SAS) involved in the activation of the stress system in the early stages of stress response. On the other hand, the tetracyclic triterpenoids (Elyakov and Ovodov 1972; Ghosal et. al. 1989), such as cucurbitacin R diglucoside (Panossian et. al. 1997, 1999) and ginsenoside Rb 1 (Wang and Lee 2000) are structurally similar to the corticosteroids which are stress hormones involved in the inactivation of the stress system and in protecting the organism from over-reaction in response to stressors (Munck et. al. 1984; Tache and Rivier 1993; Chrousos et. al. 1995; Panossian et al. 1999; Fink 2000). In this context, extracts of roots and rhizomes of *E. senticosus* and *R. rosea*, as well as extracts of berries of *S. chinensis*, belong to the first group of adaptogens, while extracts of roots of *B. alba* and *Withania somnifera* are members of the second

group (Wagner et. al. 1994; Wagner 1995). Accordingly, there is a difference in the mode of action and the pharmacological activity of the various adaptogens (Kudrin and Rodina 1986; Boon-Niermeijer et. al. 2000).

Available documentation strongly suggests that one should use extracts, i.e. mixtures of active substances, rather than pure substances in order to obtain the highest efficacy. Extension of this line of reasoning has led to the concept of a fixed combination of standardised extracts based on the adaptogens from *E. senticosus*, *R. rosea* and *S. chinensis* and known as ADAPT-232: this is the active ingredient of the Swedish registered herbal medical product chisan (Swedish Herbal Institute) which has been popular in Scandinavia in recent years.

Mechanisms of Action of Adaptogens

The mechanisms of action are difficult to define and to rationalise. It is clear (Panossian et. al. 1999), however, that the mechanisms are related to the regulation of the stress system – neuroendocrine – immune complex (Selye 1950; Chrousos and Gold 1992; Chrousos et. al. 1995; Fink 2000) and are associated with the biochemical adaptation of cells and living organisms to stress (Meerson 1981; Hochachka and Somero 1984). Stress itself is a defence response of an organism to external factors (strain) which results in the stimulation of formation of endogenous activating messengers such as catecholamines, prostaglandins, cytokines, nitric oxide (NO), PAF, etc that in turn activate the energetic and other resources of the organism and induce diseases. This is the so-called "stress-executing" complementary (switch-on) system involving the SAS (in acute response and adaptation) and the hypothalamus – pituitary – adrenal (HPA) axis (in long term adaptation), as well as various mediators at the cellular, organ and system level. Counteracting these switch-on signals is the so-called "stress-limiting" (switch-off) system which protects cells and the whole organism from over-reacting to the activating messengers. This system includes some important enzymes and mediators of intra- and extra-cellular communications at the cellular (anti-oxidant system - superoxide dismutase, catalase, glutathione-peroxidase, eicosanoids, NO), organ (eicosanoids, NO) and system levels [corticotropin-releasing factor (CRF), corticosteroids, prostaglandin E_2, NO].

When the stress system is in the normal state (homeostasis) the activities of the switch-on and switch-off systems are in balance at a certain level of equilibrium which reflects the "reactivity" of the stress system, i.e. its sensitivity to a stressor and the degree of protection of the organism against damaging effects. In the process of adaptation to the effects of a stressor, the reactivity is decreased as a result of an increase in the basal levels of the mediators of the switch-on and switch-off systems resulting in transition to heterostasis (Fig. 1). Plant adaptogens can thus be defined as agents which reduce the damaging effects of various stressors by virtue of a reduction of the reactivity of the host defence system (Panossian et. al. 1999): they adapt an organism to the stress and have a curative effect in stress-induced disorders. The primary site of action of adaptogens is thus the HPA axis where the key mediators are tropic hormones [e.g. adrenocorticotropic hormone (ACTH)], releasing hormones (e.g. CRF), corticosteroids, sex hormones, catecholamines, eicosanoids and NO. The secondary sites of action are the liver and components of the immune and cardiovascular systems where the key mediators are peroxides, eicosanoids, cytokines, NO, c-GMP and c-AMP.

There is plethora of evidence indicating that single-dose administration of adaptogens activates corticosteroid formation, and that sub-chronic pre-treatment with adaptogens normalises the stress hormone levels (Dardymov 1976; Panossian et. al. 1987). The increase in corticosteroid secretion is an evidence of the stress-protective response of the organism in order to protect itself from over-reaction to stress factors (Panossian et. al. 1999). It is known that the level of corticosteroids increases as a result

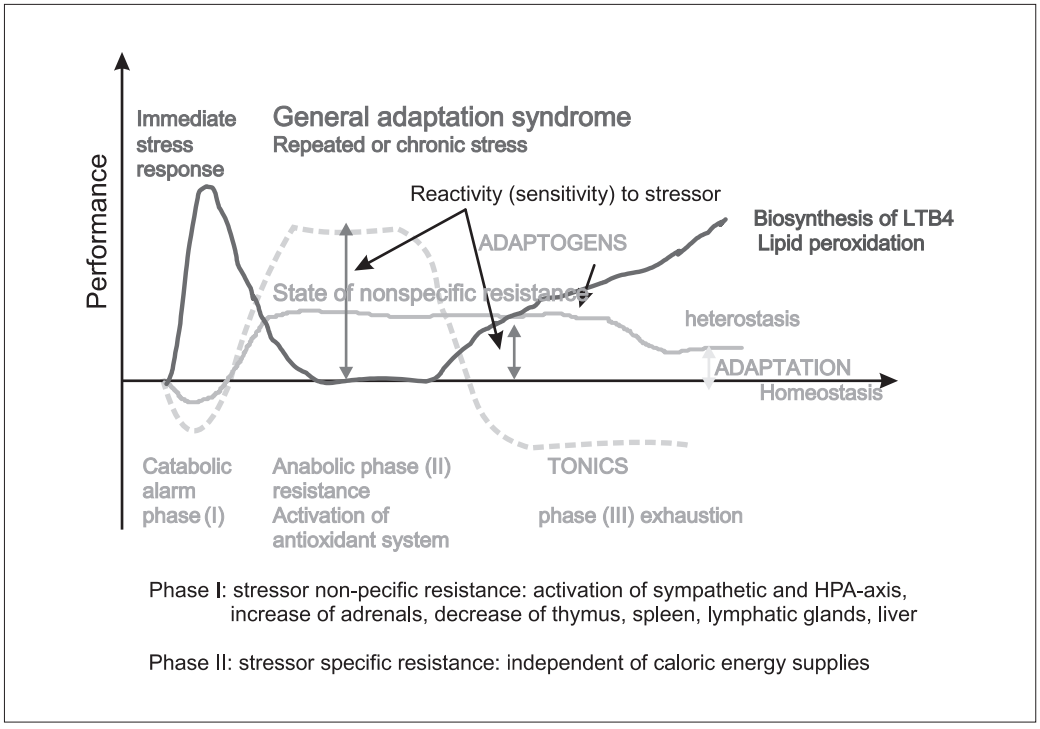

Figure 1. Immediate stress response and the effect of adaptogens.

of long-time training or adaptation, and that a trained organism responds insignificantly to stress signals by virtue of the increased activity of the hypothalamus – hypophysis – adrenal axis (HHA). In contrast, the activation of the HHA by stress in an untrained organism is very pronounced (Viru 1981). In animals that had been treated with adaptogens (Panossian et al. 1987, 1999), a moderate increase in the production of corticosteroids could be observed and, as a result of adaptation to the pro-stressor effects of adaptogens, further stress effects did not induce an acute increase in the formation of corticosteroids as was detected in control groups which had received placebo instead of adaptogens.

A recent study involving athletes has shown that stress, in the form of acute physical exercise, activates the formation of cortisol and NO in blood plasma and saliva of beginners and of more sedentary subjects (Panossian et. al. 1999). On the other hand, chronic physical exercise, as experienced by well- and long-trained athletes, increases the basal levels of these stress mediators in blood and saliva, and acute physical loading does not then increase the levels of cortisol and NO in such athletes. Plant adaptogens present in *S. chinensis* and *B. alba* show pro-stressor effects in that they activate the formation of both cortisol and NO in blood and saliva, and this activation then adapts the organism to further heavy physical loading. Thus, adaptogens increase the production of both deactivating (cortisol) and activating (NO) messengers of the stress system and are hence challengers of the defence response of the organism. In other words, adaptogens increase the capacity of the stress system to respond to external signals at the higher level of the equilibrium i.e. heterostasis. It is noteworthy that, following treatment with adaptogens, physical exercise does not increase both NO and cortisol levels in saliva. Furthermore, in subjects which have already adapted to chronic heavy physical exercise (e.g. the well-trained athlete) and with increased basic levels of cortisol in blood or saliva, the stress of physical exercise as well as the application of adaptogens can have an opposite effect, namely, a decrease in NO and cortisol levels probably

owing to their increased utilisation.

Tests carried out using developing snail (*Lymnaea stagnalis*) embryos, silk worm (*Bombix mori*) larvae, Reuber H35 hepatoma and isolated cardiac cells (Chernykh et. al. 1985; Boon-Niermeijer et. al. 2000) have shown that the adaptogens present in *E. senticosus, S. chinensis, R. rosea* etc are able to enhance resistance against a number of different stress conditions i.e. cold-induced viral infection, infection by *Bacillus thuringiensis*, formalin, heat, oxidative stress induced by menadione, and toxic ions (Cu^{+2}, Cd^{+2}, Hg^{+2}). The degree to which resistance was enhanced depended on the type of stressor applied. The results confirm that these adaptogens are universal enhancers of non-specific resistance in living organisms at various levels of organisation. It seems clear that they can adapt cells and organisms to stress by mechanisms associated with biochemical adaptation (Hochachka and Somero 1984).

Pharmacological Assessment of Adaptogens

Typically, the pharmacological assessment of adaptogens has included evaluation of stimulation, tonic and stress-protective activities. The most important feature in the pharmacological profile of adaptogens is that they increase the resistance of animals to physical exhaustion and other stresses, such as freezing, heat, altered atmospheric pressure and oxygen content, immobilisation, radiation, toxic drugs and chemicals, noise, starvation, anxiety, fear, and chronic diseases.

The effects of adaptogens on resistance to stress have been studied by evaluation of:

(i) ATP, creatine phosphate hexokinase, glycogenesis etc in dynamic and static physical performance tests (swimming, running, holding); (ii) the prevention of formation of stomach ulcers induced by immobilisation, aspirin, cold stress, etc; (iii) the prevention of decrease of weight of the thymus and increase of weight of adrenals induced by immobilisation and other stresses; (iv) the duration of simple and complex reflexes of animals after ischemia and reperfusion; (v) the prevention of decrease in milk-induced leukocytosis; (vi) the improvement in survival against toxic chemicals or bacteria; (vii) the improvement in emotional behaviour of animals; (viii) the improvement in cognitive abilities; (ix) the improvement in coordination functions; (x) the prevention of increase in locomotor activity; (xi) the prolonged maintenance of body temperature during cold stress; (xii) oxygen consumption and ECG parameters during physical loading; (xiii) the recovery of ECG parameters during physical stress; and (xiv) the NO content in blood, saliva and exhaled air during physical loading.

Endocrine activity tests have included the determination of the effects of adaptogens on the levels of: (i) ACTH, CRF, and steroid hormones in blood, adrenal cortex and other endocrine tissues and cell cultures in various *in vivo* and *in vitro* models; (ii) free arachidonic acid (AA), prostaglandin E_2, leukotrienes (LTB4) and other AA metabolites in adrenals, brain, adrenocortical cells and blood using i*n vivo* and *in vitro* models; (iii) catecholamines in blood, adrenals, brain and cell cultures in various *in vivo* and *in vitro* models; and (iv) NO in blood, saliva, adrenals, brain and cell cultures using *in vivo* and *in vitro* models. It has also been shown that NO donors increase (NO synthesis-inhibitors reduce) the duration of swimming of rats with load, decrease survival of rats and their longevity in hypoxia, and increase stomach ulcers induced by immobilisation (Malishev and Manukhina 1998).

Anabolic activity tests have included assessment of the increase of body weight and accelerated growth, as well as the increase of DNA, RNA and protein synthesis. CNS activity tests have included swimming and Rota-rod treadmill running tests, tests of evaluation of improved reflexes after ischemia and reperfusion, and catecholamine metabolism assays (COMPT inhibition). Immuno-tropic activity tests have included: (i) measurement of the level of corticosteroids, prostaglandins, leukotrienes, cytokines, and NO in blood or in various blood cells;

(ii) phagocytosis tests (chemiluminescent); (iii) flow-cytometry studies of blood cells, T_h/T_s, NK, granulocytes, monocytes, and macrophages. Anti-oxidant activities have been determined through assay of lipid peroxidation.

Effects of Adaptogens on the Central Nervous System

Experimental pharmacology

Whilst the most important characteristics are common to all adaptogens, their effects may be different in various circumstances. The effects of two of the most interesting adaptogens, namely, *Schizandra chinensis* Bail. and *Rhodiola rosea* L., on the CNS are discussed below.

The suggestion that adaptogens may stimulate the CNS was originally made in order to explain the stimulating effects of these agents on physical and mental performance in numerous experiments involving animals (Lupandin 1965, 1989; Aksyonova 1968; Ovsyanikova 1970; Lupandin and Lapajev 1981; Lupandin et. al. 1986) and humans (Astanin et. al. 1943; Karo 1945; Lazarev 1946; Murtazin 1946; Lebedev 1951a, 1967; Eglit et. al. 1965; Korolevich and Lupandin 1967; Levchenko 1971; Lupandin and Lapajev 1981; Lapajev 1982). It has been shown that small doses of an extract of *R. rosea*, or of its active ingredient rodosin at a dose of 2-4 mg/kg, increased the spontaneous bio-electrical activity of the brain, presumably by direct effects on the ascending and descending reticular formation in the brainstem (Saratikov et. al. 1965, 1978; Marina 1968; Marina and Alekseeva 1968; Saratikov 1973; Kurkin and Zapesochnaya 1986). Unlike tranquillisers, however, medium range doses of adaptogens enhanced the development of conditioned avoidance reflexes in rats and facilitated learning based on emotionally positive reinforcement (Saratikov et. al. 1965; Saratikov 1973).

Using the maze method with negative (punitive) reinforcement, it has been shown that application of an extract of *R. rosea* in a single dose of 0.1 mL per rat essentially improved learning and retention after 24 h. Significant improvement in long-term memory was also established in memory tests performed 10 days after treatment with the same dose of extract (Lazarova et. al. 1986; Petkow et. al. 1986). Ten days after oral administration of an aqueous extract of *R. rosea* at a dose of 0.1 mL per rat (body weight 180-200 g), the levels of norepinephrine (NE), dopamine (DA) and serotonin (5-HT) in the brainstem of the experimental animals rose considerably compared to the levels in the same cerebral structure in control animals. In the cerebral cortex, the levels of NE and DA decreased significantly whilst the 5-HT level increased sharply. In contrast, in the hypothalamus of rats treated with extracts of *R. rosea*, the formation of NE and of DA increased about 3-fold compared to the control group, whilst the 5-HT content decreased (Stancheva and Mosharrof 1987). Treatment with adaptogen also enhanced the effects of neurotransmitters on the brain by increasing the permeability of the blood brain barrier to precursors of DA and 5-HT.

It may be concluded that treatment with extracts of *R. rosea* promotes release of NE, DA and 5-HT in the ascending pathways of the brainstem thus activating the cerebral cortex and the limbic system. Consequently, the cognitive functions (thinking, analysing, evaluating, calculating and planning) of the cerebral cortex, and the attention, memory and learning functions of the prefrontal and frontal cortex, are enhanced. Other neuronal systems also contribute to the various aspects of memory such as encoding, sorting, storage and retrieval. The cholinergic system, for example, involves the neurotransmitter acetylcholine (Ach) and contributes to memory retrieval via pathways ascending from the memory storage systems of the limbic system to various areas of the cerebral cortex. Agents which block Ach suppress the activity of these ascending pathways and thus interfere with memory. The deterioration (partial blocking) of these systems with age results in age-associated memory loss.

Treatment with extracts of *R. rosea* can reverse this type of block (Brown et. al. 2002) and may prevent or ameliorate some age-related dysfunction in these neuronal systems.

With respect to preparations from *S. chinensis*, initial experiments with frogs indicated that the plant contains a unique group of stimulators which do not have direct anti-hypnotic effects on the CNS (unlike phenamine, caffeine etc) (Lazarev 1946). Schizandra extract induced a relative decrease in reflector activity of the spinal cord in frogs which was more prolonged than the excitation induced by other chemicals (Zhestyanikov 1945). The anti-narcotic effect of Schizandra extract became clear following experiments in which the spinal cord of a frog was preliminary suppressed by ethanol: however, the active components in the Schizandra extract delayed, but did not prevent, the narcotic effect of ethanol (Zhestyanikov 1945; Lazarev 1946). Similar effects have been observed in experiments on rabbits: in this case the chloral hydrate-suppressed reflex could be eliminated by a fatty oil extract of seeds of *S. chinensis* (Kuznetsova 1958).

Schizandra preparations show significant effects on processes of excitation and inhibition in the higher brain structures and in the spinal cord of experimental animals: such effects are: (i) an increase in spinal reflexes and motor activity of the part of the body innervated with the CNS in dogs (Pozdnyakov 1945; Lupandin and Lapajev 1981); (ii) a decrease in the latent period of reflex in frogs (Pozdnyakov 1945; Zhestyanikov 1945; Lazarev 1946; Lebedev 1951b; Kuznetsova 1958; Lupandin and Lapajev 1981), in rabbits (Voyevodina et. al. 1952; Kuznetsova 1958), and in dogs (Yefimova et. al. 1954, 1955); (iii) a widening of the range of assimilation of rhythms by the cerebral cortex (Sorokhtin and Minut-Sorokhtina 1958); elimination of the inhibition of bio-electrical activity of the cortex and sub-cortical structures induced by berbamyl, chloral hydrate or aminazine (Volicer et. al. 1966a); (iv) prevention of the narcotic effect induced by sodium amytal in rats - the effect was stronger when a seed extract of *S. chinensis* was administrated 0.5 h before the amytal compared with treatment where the extract was given at the same time as, or after, the administration of amytal (Petkov 1956).

It has been suggested that Schizandra preparations can have a stimulating effect on the CNS by increasing the excitability of the neuronal cells, intensification of excitation processes and other events (Lazarev 1946; Lupandin and Lapajev 1981): treatment with Schizandra extract also induces sleeplessness (Pozdnyakov 1945). A dose-dependent reversal effect on conditioned reflexes in dogs has been observed: in low doses, Schizandra extract has a stimulatory effect improving the conditioned reflex activity, but in higher doses it exerts a negative effect on the higher nervous activity of dogs disturbing the complex conditioned reflex activity (Voyevodina et. al. 1952). The petroleum ether extract of the fruits of *S. chinensis* mainly effects the cholinergic system, and this effect is biphasic: small doses decrease the threshold for nicotine convulsions, potentiate the anti-diuretic effect of nicotine and the effect of carbachol on intestinal motility, whereas higher doses have a cholinolytic effect. In contrast to other psychomimetic substances, Schizandra extract does not antagonise the effects of reserpine (catalepsy, eyelid ptosis, thiopentone anaesthesia in mice) but can even enhance the effects (Volicer et. al. 1965, 1966b).

It has been shown that schizandrin is the main active principle of *S. chinensis*: this compound may: (i) stabilise the bio-electric activity of the cerebral cortex at a dose of 1 mg/kg whilst showing an activating effect at doses of 2-3 mg/kg; (ii) directly excite upraised activating system at a dose of 2-3 mg/kg; (iii) recover the bio-electric activity of the cerebral cortex which has been suppressed by chloral hydrate, berbamine or aminazine at doses of 5-10 mg/kg; (iv) increase spinal reflexes in rabbits and decerebrated cats (Lebedev 1967); (v) inhibit development of new conditioned reflexes in mice; (vi) enhance the convulsive effect of corazole and

strychnine; and (vii) extend the duration of hexenal and chloral hydrate induced sleep in mice (Lebedev and Kamilov 1966).

Inhibition of inactivation of catecholamines (catechol-0-methyl-transferase; COMT) in adrenergic synapses.

A principal hypothesis concerning the mechanism of action of the active principles of *S. chinensis*, i.e. the lignans, involves the inhibition of COMT, an enzyme which, along with monoamine oxidases, inactivates catecholamines. Inhibition of COMT results in an increase in duration of activation of the adreno-receptors: exhaustion of the catecholamine deposit does not occur, and the release of catecholamines from nerve endings of the sympathetic nervous system decreases (Lupandin and Lapajev 1981; Lupandin 1991). However, this hypothesis is not supported by incontrovertible evidence since much of it is indirect.

One finding is that Schizandra preparations interact with known competitive and non-competitive inhibitors of COMT (i.e. apomorphine and pyrogallol) in experiments involving mice with apomorphine-induced hypothermia and increased duration of stereotypic movements (Lupandin and Lapajev 1981). The lignans in Schizandra extract increased significantly the apomorphine-induced duration of stereotypic movements of mice particularly after administration of precursors of catecholamines (i.e. L-DOPA) (Lupandin 1989). A second piece of evidence is based on the observation that COMT inhibitors increase the sensitivity of the organism toward catecholamines: it has been found that the LD_{50} of epinephrine is lower in mice treated with Schizandra extract (Lupandin and Lapajev 1981). However, no reports are available concerning the effect of Schizandra extract on the biosynthesis of catecholamines or on COMT activity. It has only been reported that the concentration of catecholamines is not changed in brains of animals following administration of Schizandra preparations (Volicer et. al. 1966b).

Effects of schizandrol A on monoamine neurotransmitters in the CNS.

It has been shown that schizandrol A (a lignan present in Schizandra extract) exerts inhibitory effects on the CNS. For the purposes of elucidating the mechanism of this inhibition, the concentrations of monoamine neurotransmitters and their metabolites in rat brain and the effects of schizandrol A on some receptors were determined by ion-pair reversed-phase liquid chromatography using electrochemical detection and a competitive binding assay. In the neurotransmitter studies, significant elevations of DA and its metabolite dihydroxyphenylacetic acid (DOPAC) in striatum, and DA in hypothalamus, were observed after interperitoneal administration of 50 or 100 mg/kg of schizandrol A. However, the receptor binding experiments showed that schizandrol A had no affinity for dopamine D1 and D2 receptors, serotonin receptors, or alpha 1- and alpha 2-adrenergic receptors, and it did not affect the binding of DA to dopamine D1 or D2 receptors. These results indicate that the inhibition exerted by schizandrol A on the CNS may be related to the DA system, and the increase of DA turnover has nothing to do with dopamine receptors. The concentrations of the NE metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) and the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) showed changes in rat striatum and hypothalamus after treatment with schizandrol A, but NE and serotonin levels themselves were unaffected (Zhang and Niu 1991).

Studies on healthy subjects

The stimulating effect on working capacity and mental performance.

An initial study on healthy subjects (33 marines) showed that, compared with a control group (given a German chamomile decoction), a Schizandra extract did not have any anti-hypnotic effects unlike other stimulants (i.e. phenamine, caffeine) (Lazarev 1946).

However, Schizandra extract can induce a reduction of chronaxy as demonstrated by experiments on neuro-muscular excitability in 13 healthy subjects (Yefimov and Vlasova 1945).

In a case report on the effects of Schizandra extract on excitation and inhibition of reflexes in post-traumatic encephalopathia, it was suggested that the positive therapeutic effect of the preparation was due to the correction of imbalance in excitation and inhibition of reflexes (Markova and Samoilova 1954).

Following ingestion of capsules containing powdered seeds of *S. chinensis*, the stimulating effect commenced within 2 - 2.5 h, increased to a maximum value at 3.5 h and disappeared in 5.5 h (Kokhanova et. al. 1950). A more pronounced tonic effect was observed in fatigued subjects who were subjected to ergographic tests whilst sawing wood (for 5 min with a frequency of 45 movements/min): according to the Dubua test, working capacity was increased from 27.5 kg/m (control) up to 77 kg/m in the treated group (Kokhanova et. al. 1950). Long-term treatment with seeds of Schizandra (1g/day) was effective only for the first 10 days (Kokhanova et. al. 1950; Yefimova et. al. 1954).

A comparative study involving highly qualified athletes (62 oarsmen) and non-trained subjects (58 soldiers) showed that Schizandra extract (at a dose of 2 g/day) increased PWC_{170} (step ergometric test) in both groups: however, whilst the increase was observed in the first few days of the study in the non-trained subjects, in the athletes the increase was obvious only after 7 or more days of drug uptake (Lupandin 1990).

Schizandrin increased the working capacity of 20 year-old athletes running over a distance of 3000 m. In all tested doses (5, 10 and 20 mg) the stimulating effect of schizandrin was of the same magnitude as that of phenamine, and the average running time (1 min 42 s; n = 129) of the treated group of athletes was remarkably better than that of athletes of the control group treated with placebo (glucose) (Lebedev 1967, 1971).

Extremely promising positive effects of Schizandra extract on adolescents working in a factory environment have been reported (Yefimov and Vlasova 1945), with opposite effects, at the same dosage, on the negative factors (suppressed muscular activity, depression and sleepiness) experienced in high temperature workshops.

A single dose of Schizandra tea produced a tonic effect in sailors (n = 200) keeping watch for at least the first 7-10 days of daily treatment. However, following 2-3 weeks of continuous use of the tea, some subjects developed sleeplessness, excitability and low general well-being. These negative side effects could be eliminated by interruptions with black tea (Grigorenko and Berdyshev 1988).

In a duplicated set of experiments involving telegraph operators between the ages of 21 and 24 years (n_1=20, n_2=23) it was shown that single doses of Schizandra extract (10% in 70% ethanol; 30 mL) and schizandrin (5, 10 and 20 mg) prevented exhaustion-related errors in Morse-broadcasting at maximum speed for 5 min: the frequency of errors in the control groups (given a placebo of either glucose or 70% ethanol) was 130% whilst errors in the treated groups were 84-103% (errors in the first control test were normalised at 100%). Similar results were obtained with Ginseng and phenamine: however, the latter produced an effect of excitation which increased speed but not performance (Lebedev 1967).

The effects of Schizandra extract on the mental working capacity in humans was studied by a method of text correction in which fatigue decreased the accuracy but not the speed of work (Lebedev 1951a,b). Examination of students (n=59) taking powdered seeds of *S. chinensis* showed an improvement in work in 38 subjects (65%), with an increase in the amount and an improvement in the quality of correction in 17 subjects, an improvement only in the quality of correction in 14 subjects, and an increase only in the amount of work performed in 7 subjects (Kochmareva 1958). Further screening of six constituents isolated from the extract using this test (n=20; each subject tested with all compounds)

showed that schizandrin was the most active substance. At a dose of 3.6 mg, schizandrin prevented exhaustion-related errors in text corrections by human subjects: the errors in the control group (with placebo) were 228%, whilst the errors in the group treated with schizandrol were 95% (errors in the first control test were normalised at 100%) (Lebedev 1951a,b, 1967).

A comparative study of Schizandra extract and other adaptogens (Eleutherococcus, Aralia, Echinopanax and saparal) on the functional state of helicopter crews (665 observations on 87 pilots, navigators, mechanics and radio-operators; 15 subjects in each group) has been carried out. The subjects took the test preparation (or a placebo) at a dose of 1 mL twice a day for 10 days and were tested before a flight and 5-15 min, 1 h and 3 h after landing. The psycho-physiological state of each subject was evaluated by seven tests including assessment of dynamic tremometry, sensomotor response, memory and attention performance. None of tested adaptogens prevented the decrease in functional state which was recorded immediately after landing, however, they were effective in speeding up the restoration and elevation of the basal level of this functional state (Gubchenko and Fruentov 1986). The most effective adaptogen was Aralia, whilst the least effective was Schizandra.

Rodelim (a fixed combination of standardised extracts of *S. chinensis, Eleutherococcus senticosus* Maxim and *R. rosea*), when applied in repeated or single-dose format, has been shown to increase significantly the mental working capacity of healthy volunteers (computer operators on night duty at the Department of Systems of Life Activity Provision, Rescue and Protection on Aircraft; n=60) in experiments which simulated long monotonous activity inducing fatigue (Vezirishvili et. al. 1999; Roslyakova et. al. 2000). The assessment of the effect of rodelim was based on a study of the psycho-emotional and psycho-physiological states, the professional and mental working capacity, and the cardiovascular system. Methods of evaluation included mathematical analysis of the cardiac rhythm, computer tests, questionnaires and psycho-physiological tests, ophthalmologic examination, and medical tests (heart rate, ECG and respiration parameters, blood pressure, etc). Rhodelim has been recommended for increasing mental and physical performance and working capacity under high load such us long work periods with computers, night duty, monotonous activity, etc (Vezirishvili et. al. 1999; Roslyakova et. al. 2000).

The effect of a repeated low-dose treatment (170 mg/day) of a standardised extract (SHR/5: standardised to 3% rosavin and 0.8% salidroside; Swedish Herbal Institute, Goteborg, Sweden) of *R. rosea* rhizome (RRE) on fatigue during night duty amongst a group of 56 young, healthy physicians was investigated in a double-blind placebo-controlled randomised cross-over study. The effect was measured in terms of total mental performance calculated as a total fatigue index: the tests chosen reflected an overall level of mental fatigue, involving complex perceptive and cognitive cerebral functions such as associative thinking, short-term memory, calculation, ability to concentrate, and speed of audio-visual perception. These parameters were tested before and after night duty during three periods each of two weeks, namely, (i) a test period of one RRE/ placebo tablet daily; (ii) a wash-out period; and (iii) and a period of one placebo/RRE tablet daily, in a double-blind cross-over trial. A statistically significant improvement in the results of 5 different tests measuring perceptive and cognitive cerebral functions was observed in the RRE group during the first two week period and no side effects were reported. These results suggest that RRE can reduce general fatigue under certain stress conditions (Darbinyan et. al. 2000).

Spasov and co-workers compared the effects of an *R. rosea* extract (SHR-5; 100 mg/day) with placebo in a double-blind 20-day study of Indian medical students (n=60) studying in Russia during their final exam period. Despite the low dosage, investigators found significant improvements in general

well-being, physical fitness, mental fatigue, final exam grades, and coordination, but not in some aspects of cognitive functioning, in students taking SHR-5 compared those taking the placebo.(Spasov et. al. 2000a,b).

A randomised, double-blind, placebo-controlled, parallel-group clinical study with an extra non-treatment group, was performed on cadets in order to measure the effect of a single dose of standardised SHR-5 extract on the capacity for mental work against a background of fatigue and stress. An additional objective was to investigate a possible difference between two doses, one dose being chosen as the standard mean dose in accordance with well-established medicinal use of the extract as a psychostimulant/adaptogen, the other dose being 50% higher. Various physiological parameters, e.g. pulse rate, systolic and diastolic blood pressure, were also measured. The study was carried out on a highly uniform population comprising 121 cadets aged from 19 to 21 years, and all groups were found to have very similar initial data, with no significant differences in any of the parameters. The study showed a pronounced anti-fatigue effect of SHR-5 as determined by a defined anti-fatigue index ratio (AF1). The verum groups (treated with 2 and 3 capsules, respectively) showed mean values for AF1 of 1.0385 and 1.0195, whilst the mean AF1 for the placebo group was 0.9046. Statistically the results were highly significant ($p < 0.001$) for both dosage groups compared with the control groups, although no significant differences between the two dosage groups were observed. There was a possible trend in favour of the lower dose in the psychometric tests, but no such trend was found in the physiological tests (Shevtsov et. al. 2003).

In a double-blind placebo-controlled study of 60 foreign students at a Russian high school, administration of an extract of *R. rosea* (rodaxon: 660 mg/day) resulted in an increase in physical (velergometric) work capacity, coordination, kinesthetic sensitivity, and general well-being along with a decrease in psychic fatigue and situational anxiety (Spasov et al. 2000a,b): unfortunately, this study provides no information on the amount of *R. rosea* in the rodaxon preparation.

Clinical pharmacology

An excessive basal and/or stress-responsive activity of the stress system is associated with increased arousal or anxiety, increased blood pressure, gastrointestinal dysfunction, and immune suppression (Chrousos et. al. 1995). Both the HPA axis and the SAS system appear chronically activated in melancholic depression which is characterised by hyperarousal (anxiety) and suppression of feeding and sexual behaviour (anorexia, loss of libido), and an excessive and prolonged redirection of energy with tachycardia and hypertension as classic manifestations of the generalised stress response. Chronic activation of the HPA axis has also been shown in other conditions such as anorexia nervosa, panic anxiety, obsessive-compulsive disorder, chronic active alcoholism, alcohol and narcotic withdrawal, excessive exercising, malnutrition, and in sexually abused girls.

On the other hand, chronically decreased basal stress-responsive activity of the stress system is associated with decreased arousal, sub-optimal physical and mental performance, and a decreased feeling of well-being. Seasonal depression in the dark months of the year, in the postpartum period, in chronic fatigue and in fibromyalgia syndromes represent this state, and under these conditions CRF secretion is decreased, and symptoms such as increased appetite and weight gain, somnolence and fatigue are often observed (Chrousos and Gold, 1992).

Rhodiola rosea L.

Asthenia and psychiatric disorders

In 1969 the Pharmacological Committee of the Ministry of Health of the USSR recommended the

medicinal use and the industrial production of a liquid extract of *R. rosea*. Through order number 933, October 13, 1975, the Ministry of Health of the USSR registered the preparation (No. 75/933/14) and allowed its production for medical use under the name of Rhodiola extract, liquid. Its curative effect was tested in 53 healthy subjects and in 412 patients with neuroses, vascular dystonia, hypotension, schizophrenia with remissions of asthenic type and asthenia syndromes of functional and organic genesis. The Rhodiola extract was prescribed in a dose of 5-25 drops in a quarter of a glass of water 3 times a day, 15-30 min before meals. The duration of the therapy was individually determined and varied from 10 days to 4 months.

During the first stages of the clinical studies the therapeutic dose of Rhodiola extract was verified. It was found that an increase in the dose to 30-40 drops induced high irritability, insomnia, unpleasant sensations in the heart region and, finally, the signs of ultimate inhibition in some patients on the second and third days of the therapy. Owing to its psycho-stimulating and adaptogenic properties, Rhodiola extract was found to be a valuable medicine for essentially healthy people with some tendency to asthenisation when they were performing tasks requiring high mental exertion (Krasik et. al. 1970a,b). Asthenisation was manifest in their reduced working capacity, difficulties in falling asleep, poor appetite, irritability and headaches. Similar symptoms were frequently observed in these subjects after intensive work requiring high levels of mental exertion. However, these asthenic symptoms developed without psychogenia and were not accompanied by a complex of disorders when neurasthenia could be diagnosed.

With respect to asthenia prophylaxis, 27 essentially healthy students, doctors and scientific workers of age 19-46 years were prescribed Rhodiola extract (5-10 drops) in the morning, or in the morning and afternoon, for 2-3 weeks starting a few days before periods of intensive mental work and during the whole period of considerable mental exertion (for example, examination sessions for students, commencement of work on a project, etc). In all cases, therapy with Rhodiola extract for several days in succession prevented asthenic decompensation when the subjects were carrying out work requiring long intensive mental activity.

The positive therapeutic effect of Rhodiola extract was also observed in patients with pronounced asthenia states of different genesis (Krasik et. al. 1970a,b). Patients (128) of ages 17-55 year (53 females and 75 males) were treated with the extract and as a result clinical symptoms of the asthenia syndrome (i.e. general weakness, reduced working capacity, low memory, increased diversity, irritability, headaches, insomnia, autonomic dysfunctions) improved considerably or disappeared completely in 81 patients (64%). Subjective improvement of the state of patients was confirmed by the results of a psychological examination and the increase in their working capacity. The therapeutic effects of Rhodiola extract on asthenic states caused by psychogenic and somatogenic reasons [mainly neurasthenia (82%) and asthenia convalescents after somatic and infectious diseases (80%)] were the most pronounced: for example, patients in a state of asthenia after influenza felt less tired and sleepy during the day, felt less flaccid, and showed improved mental and physical working capacity by the third day of therapy with Rhodiola extract. Patients receiving this treatment could concentrate their attention much better and their headaches were reduced or disappeared. Whilst the therapeutic effect of Rhodiola extract on asthenic states of purely organic genesis was not revealed, this does not apply to traumatic cerebrasthenia with a duration of the disease of up to 5 years: in such cases, Rhodiola extract not only reduced or eliminated general weakness and fatigability, but clearly facilitated the normalisation of the autonomic functions in this group of patients (in 67% of cases).

The administration of Rhodiola extract within a complex supportive therapy is totally justified as such a combination can improve and stabilise remissions of an asthenic type in schizophrenia patients. Therapy for such patients should continue for at least 1-2

months. Catamnestic observations showed that the most pronounced therapeutic effect was achieved in patients with periodic and paranoid (with coat-like development) forms of schizophrenia in a state of remission of the asthenic type. This was manifest in the reduction of flabbiness, the broadening of interests, and an increase in the productivity of the mental and physical work of the patients: patients also reported that they felt more energetic (Saratikov and Krasnov 1987).

Clinical studies of the dynamics of the reverse development of asthenic symptoms showed that Rhodiola extract was able to sooth or eliminate depressive and hypochondriac symptoms frequently accompanying or included in the asthenic complex of symptoms in cases of astheno-depressive and astheno-hypochondriac states of different nosology, including schizophrenia. When asthenia was combined with paranoid suffering or deep emotional changes, Rhodiola therapy had no effect.

Similar results were obtained by Mikhailova (1983) in a clinical patho-psychological study of the efficacy of Rhodiola extract in 58 patients with asthenia of exogenous organic genesis. The preparation was prescribed in doses of 15 and 25 drops, 3 times a day for a month (some of the patients took the preparation for up to 4 months). General weakness, the feeling of being worn out in the morning, high fatigability, and hypersomnia during the day (without disturbance of the following night's sleep) either disappeared or became considerably reduced when Rhodiola extract was taken at a dose of 15 drops. Typically, no side effects were observed after this dose: in only one patient (out of 28) was sleep disturbed, and anxiety and internal restlessness appeared at the third week of the therapy. In this case, the dose was reduced to 6 drops twice a day and the adverse symptoms immediately disappeared. Sleep improved during this therapy for most of the patients (39 out of 58) with pre- and intra-somnia disorders (i.e. difficulties in falling asleep accompanied by hallucinations; waking up during the night) reduced. It should be mentioned, however, that both sleep normalisation and reduction of other asthenic symptoms depended on the level of these disorders and the depth of the pathological process resulting in the development of the asthenic syndrome.

During treatment, the reduction in asthenic symptoms was accompanied by the improvement of the patient's mood in most of cases. Patients became more sociable and active, and their level of motivation increased indicating, evidently, that the preparation had a thymoanaleptic effect. As a rule, the ability to concentrate active attention improved, the redistribution of attention became easier, and memory also improved in these patients. During the second and third weeks of therapy, patients reported a decrease in their sensory excitability, i.e. loud sounds and bright lights did not induce irritation, headache or the feeling of heaviness in the head, all of which symptoms had been observed before the treatment. Headaches in most of the patients with asthenic syndrome were caused by intracranial hypertension: in this aspect, it is important to note that on the seventh to ninth days of treatment the authors observed more frequent urination in parallel with a reduction in heaviness of the head, and a reduction of intensity, frequency and duration of headaches. Thirty patients took Rhodiola extract at a dose of 25 drops, 3 times a day: usually, the positive effects of the preparation were observed faster in these patients, but in some patients blood pressure increased and this was accompanied by squeezing pains in the heart region, and retrosternal pain radiating into the left arm and scapula was observed during the second and third weeks of treatment. Typically, such pains developed in patients with a tendency to coronary spasms and unstable blood pressure. More recent results of Mikhailova (1983) showed a good therapeutic effect with high doses of Rhodiola extract (30-40 drops; 2-3 times a day) in patients with the asthenic syndrome and a reduction in the symptoms of muscular weakness, high fatigability, continuous flabbiness, hypersomnia, low level of motivation, and apathy, with stable arterial hypotension prevailing in the structure of the syndrome. As soon as a reduction in the

asthenic symptoms is achieved, the dose of the extract should be reduced to 15-20 drops (for 2-3 months in the morning and during the day).

Studies carried out in 1981-1986 by Sudakov and co-workers (Sudakov et. al. 1986) also showed that Rhodiola extract has a positive effect on patients with nervous and/or mental disorders of exogenous-organic genesis. The maximum therapeutic effect was observed in cases of post-traumatic and vascular disorders of the brain in the initial stages of development of nervous mental disorders and in persons of mental and creative professions with slightly pronounced psychopathic-like and mnestico-intellectual disorders. In cases of pronounced patho-characterological disorders of an explosive or hysterical type, Rhodiola preparations should be prescribed in combination with tranquillisers and anti-depressants. In such cases the positive therapeutic effect of Rhodiola extract is the result not only of stimulating action, but of also of the prevention or reduction of development of side effects associated with treatment with tranquillisers and anti-depressants. The combination of Rhodiola extract with nootropic preparations (nootropil, pyracetam) was found effective in patients with pronounced mnestico-intellectual disorders. Rhodiola therapy of patients with explosive and euphoric types of organic dementia showed low effectiveness, and if paranoiac disorders and symptoms of alcoholism were present in the structure of the nervous-mental disorders, the state of such patients became worse, and disorganisation of the mechanisms of social adaptation were observed later.

The use of Rhodiola extract in combination with anti-depressants in the therapy of depressive states of different genesis (Brichenko et. al. 1986) reduced the length of stay of such patients in hospital. The reduction of affective and motor components of the depressive triad, the increase in general activity, intellectual and physical productivity, and even a decrease in side effects induced by tricyclic anti-depressants, were observed with this combined therapy.

Rhodiola extract was successfully used in the alleviation of side effects after psychotropic therapy in schizophrenic patients (Krasik et. al. 1970a,b). The preparation was prescribed in high doses (25-40 drops; 2-3 times a day) to 31 patients with pronounced clinical symptoms of extrapyramidal syndrome resulting from therapy by neuroleptics: the duration of the treatment was 1-1.5 months. Nineteen patients took Rhodiola extract in addition to romparkin, as this preparation alone failed to eliminate or soothe the clinical symptoms of the side effects in this group of patients. Rhodiola extract had the most pronounced therapeutic effect on symptoms of Parkinsonism, asthenia and hypotension within the akinetohypotensive and akinetohypertensive syndromes.

The pronounced therapeutic effect of Rhodiola extract has also been observed in a study of 65 patients with various forms of neuroses (Saratikov et. al. 1965). Apart from routine clinical examinations, the state of the higher nervous activity was tested in these patients with the help of a verbal test and conditional motor reflexes with verbal reinforcement. Before treatment, the patients complained of insomnia, high irritability and various somatic disorders. The results of the verbal tests showed that the latent period of verbal reactions in most of the subjects was long - up to 1.8-6 s (the normal period being 1.5 s). Polyphrasia, primitive answers, perseverations, refusals, and exhaustion of verbal reactions were observed by the end of the test. The results of the motor-verbal test showed that, before the treatment, two thirds of the patients had weakness of inhibitory and excitation processes in the cerebral cortex. In some patients, the mobility of the inhibitory process was disturbed and this was manifest in difficulties of differentiation development. After a course of therapy with Rhodiola extract (10 drops; 3 times a day for 10 days) both excitation and inhibitory processes intensified and their mobility became normal. Further, conditional motor reflexes were developed, their value and stability increased, the latent period reduced, concentration improved and generalisation of cortical excitation was limited, differentiation to positive and negative stimuli were more readily developed, and the interaction of both

signal systems became normal. The latent period of verbal reactions reduced in all patients, perseverations, refusals and polyphrasia disappeared, the answers became more informative, and attention and memory improved.

According to the authors, analysis of the nature and frequency of changes in individual parameters of the cortical activity of the subjects suggested that Rhodiola extract mainly affected the excitation process. The stimulating effect of the preparation was less pronounced in patients with a weak inhibitory process. Apart from normalisation of the nervous processes, clinical improvement in the state of the patients was also observed: irritability and unpleasant sensations in the heart region disappeared, and sleep and appetite improved, whilst blood pressure usually became normal in hypotensive patients. Similar clinical results were obtained in another study with 177 patients with vascular hypotension. After a course of therapy with Rhodiola extract, the stable, complete or partial normalisation of brachial and temporal pressure with levelling of the temporal-brachial coefficient was observed in 92% of hypotensive patients. Simultaneously the patients felt better, their headaches disappeared, sleep became normal and they recovered their working capacity.

Based on the above findings, preparations of Rhodiola were indicated in the USSR: (i) as stimulants for essentially healthy people in a state of fatigue and for patients with asthenic states during the rehabilitation period following somatic or infectious diseases; (ii) for essentially healthy people with a tendency to asthenisation during their work requiring high mental exertion: such preparations should be taken several days before the expected strain and during the whole period of raised mental exertion for the prophylaxis of decompensation of asthenic type; (iii) to recover working capacity during and after long periods of intensive physical work; (iv) in cases of borderline nervous-mental diseases, neuroses (neurasthenia, depressive neurosis, neurosis of obsessions), neurosis-like disorders of exogenous-organic and somatic origin, psychopathies (of asthenic and anancastic type), neurocirculatory dystonia of the hypotensive type, and sexual disorders related to impotence in males; (v) in psychiatric practice for complex correction of the neurological side effects of psychopharmacological therapy, especially in cases of akinetohypotensive syndrome; (vi) for schizophrenia patients within complex supportive therapy for the intensification and stabilisation of remissions of asthenic and apathico-abulic type.

As for other adaptogens, preparations of Rhodiola are recommended in folk medicine for old people in order to increase their vital capacities. The dose of Rhodiola extract is 5-10 drops in a quarter of a glass of water, taken 2-3 times a day typically 15-20 min before meals: the treatment should last 10-20 days. In psychiatric practice, higher doses (10-40 drops; 2-3 times a day) may be taken for 1-4 months. Typically, the treatment should commence with 10 drops and, if the effect is insufficient, the dose may be increased by adding 5 extra drops every 3-4 days: the total dose should not be higher than 40 drops, and the total amount taken during the day should not exceed 80 drops. In these doses, preparations should be taken 4-5 h before going to bed in order not to disturb the sleep pattern.

Rhodiola extract is contraindicated for people with very pronounced symptoms of high nervous excitability and exhaustion of cortical cells, feverish states and hypertensive crisis. Side effects of therapy with Rhodiola extract are quite rare. Some cases of individual sensitivity to the preparation have been observed including excitement, irritation, insomnia, and headache. In all such cases the therapy should be terminated.

Schizandra chinensis Bail.

Asthenia

Preparations of Schizandra (in the form of tincture, decoction and tablets) have been found to be effective in the treatment of general asthenia, exhaustion and reduced physical and mental performance with more

than 250 patients showing improvement after 2-10 weeks of therapy (Rossijskij 1952a,b). The treatment showed a particularly remarkable effect on a group of patients (n=200) with nervous disorders where an increase in general well-being and working capacity, as well as a decrease in sleepiness and flabbiness, was observed (Rossijskij, 1952a,b).

Nervosis

A comparative pilot clinical study of pantocrin, and tinctures of Schizandra seeds and Ginseng roots (10% and 3%, respectively) in neurasthenic patients (n=95) showed a high efficiency with respect to Schizandra therapy (at a dose of 15 drops for 25-28 days). General weakness, poor sleep and appetite, high irritability and headaches disappeared almost completely whilst in the control group 55% of the patients complained of these symptoms. Muscular force in the hands increased some 2.5-times in the treated group compared with the control group, and gain of vital lung capacity was 19% (3% in the control group). In addition, blood haemoglobin increased by 6% in the treated group whereas in a control group treated with standard medication it increased only by 1.6% (Farutina 1951).

Psychogenic depression, astheno-depressive states, schizophrenia and alcoholism

Positive therapeutic effects of Schizandra preparations on asternic- and astheno-depressive states (particularly in exogenous depressions) in psychiatric diseases were reported by several groups of investigators (Staritsina 1946; Sivertsev 1946, 1950; Leman 1952; Zakharov 1956; Galant et. al. 1957; Galant 1958; Romas 1958, 1967). For example, Leman (1952) found that for a complete group of 40 patients with asthenia and depressions of psychogenic or somatic origin, a stimulating effect of a Schizandra preparation [fruit and seed (1:5) tincture; 90% ethanol] on the CNS could be observed after treatment for 16-40 days. An improvement in vision in the dark, and a rush of blood to the skin and the extremities was found in almost all patients. Twenty two patients felt a pleasant warmth all over their bodies, they became energetic and physically active, the feeling of hunger and fatigue disappeared, the mood improved, and night sleep became normal: cold endurance increased in 26 patients. These results suggest that Schizandra extract is a cerebral cortex stimulant in the long term, presumably owing to inhibition (negative induction) of the sub-cortex rather than by its excitation. In 7 patients, the first 2-3 doses induced a strong effect (increased anxiety, fear, too rapid flow of thoughts, unpleasant heat in the whole body and face, restlessness, loss of appetite, insomnia and tendency to hysteria), but whilst this state continued for 8-24 h, it later disappeared and was followed by an almost total recovery with the same positive effects being observed as in the majority of patients. It was concluded that therapy with Schizandra can be indicated in asthenia and depression of psychogenic etiology (so called "exogenous" depression) or states related to excessive fatigue, somatic and nervous exhaustion, but in "endogenous" depression (organic etiology), asthenia, narcoleptic and amnestic syndromes, the therapy can only relieve the symptoms. The advantage of treatment with Schizandra is the absence of side effects: tolerance to Schizandra extract is many times higher than tolerance to caffeine or phenamine, and the effect is not reduced following prolonged treatment. Probably hot weather or long periods of time in a warm environment are contraindications for the administration of Schizandra preparations.

In another study, all 10 patients with astheno-depressive syndrome (ADS), characterised by sleepiness, flabbiness, motionlessness, fatigue, blue mood, etc, fully recovered after 10 days of treatment with Schizandra tablets (0.5 tablet before breakfast and 0.25 tablet each before lunch and dinner) (Zakharova 1948; Rossijskij 1952a,b). In all other groups of patients with schizophrenia (n=8), psychopathy with ADS (n=3) and organic CNS with ADS (n=8), the ADS was eliminated but other signs

of the diseases were not affected; moreover, in patients with psychosis and hysteria, the effect of Schizandra treatment was negative (Zakharova 1948; Zakharov 1956). In contrast, total recovery of psychosis following treatment with Schizandra extract was reported by another group of investigators (Galant et. al. 1957). In this study, 36 patients (19 with schizophrenia; 6 with reactive psychosis; 4 with alcoholic psychosis; 3 with involutional depression; and 4 with psychopathy) with ADS were treated with powdered seed of *S. chinensis* for 10 days (0.5 g; 3 times a day). Total recovery was observed in the cases of patients with psychosis, but no effects were seen in those patients with psychopathy; in the group of patients with schizophrenia, 6 patients recovered, 7 showed improvement, whilst for 6 patients (the most difficult cases) treatment with Schizandra was not effective (Galant et. al. 1957).

In other clinical trials, 60 psychic patients were investigated (Romas 1958, 1960, 1962). In a group of 31 patients diagnosed as schizophrenic (4 with simple schizophrenia, 11 paranoid, 14 catatonic hamper, and 2 catatonic excite), treatment with Schizandra was effective in the elimination of catatonic hamper, but was either not effective or had a negative effect on patients with the other forms of schizophrenia. In patients with maniacal depressive psychosis (n= 9), Schizandra treatment decreased depressions and associated hamper, but did not alter the hypomaniacal state. In hallucinogenic-paranoidal schizophrenia and alcoholic hallucinosis, Schizandra extract promoted the disappearance of hallucinations and of alcoholic deliria.

A tincture of berries of *S. chinensis* was used for the treatment of schizophrenia (41 patients) and chronic alcoholism (197 patients) by Romas (1967). Pupillary and vascular (alterations of the volume of palm vessels) tentative reactions were measured (by visual pupillometer and plethysmograph), and refectory reactions were studied in order to evaluate the effects on the CNS. In schizophrenia and chronic alcoholism, these reactions are comparatively suppressed: it was shown that treatment with Schizandra tincture normalised these reactions in the studied patients and activated them in normal subjects. As a result of treatment, patients were calm, sociable, gregarious and active, free of emotional tension and anxiety, willing to work etc, and showed excellent well-being with an associated good mood, Patients with hallucinogenic-paranoidal schizophrenia ceased suffering from hallucinations; further, sebaceous fattiness in the face disappeared, and activation of face mimic and general activity was observed in patients with catatonic hamper. Optimal doses of the tincture were reported to be 15-25 drops in simple and hallucinogenic-paranoidal schizophrenia, 5-15 drops in paranoidal schizophrenia, and 5 drops in catatonic schizophrenia (Romas 1967).

Based on the observations on 15 patients, Zakharov (1956) concluded that two administrations of Schizandra extract per day is optimal, that prolonged treatment can bring about negative effects, and that the duration of the course of treatment should be decided on an individual basis. Results of the treatment have proven to be considerably better in short term patients than in chronic patients (Romas 1967; Zakharov 1956).

Of particular of interest is the fact that, besides intensifying the excitability of the brain centres in schizophrenic patients and chronic alcoholics, Schizandra extract increases reactivity to insulin, sulphadiazine and apomorphine. Thus administration of a Schizandra preparation together with apomorphine frequently eliminated or decreased addiction to apomorphine: by the end of the treatment a stable conditional emetic reflex developed in most of the chronic alcoholics (Romas 1962, 1967).

It was also found that activity of the second signal system and its interaction with the first signal nervous system were considerably activated in Schizandra-treated schizophrenic patients (n=32) and in chronic alcoholics (n=16). Thus, Schizandra therapy intensified the development of conditioned reflexes to one or two parameters of the geometrical figures presented to the subjects and verbalisation of the action by the subjects was also improved. Schizandra

treatment increased associative process in the subjects and improved the quality of associations as demonstrated by the increased number of higher verbal responses and a decrease in the number of lower responses (Lastovetskij and Romas 1963).

Another interesting finding, which appears to be of much practical importance, is that a combination of Schizandra therapy with tranquillisers or anti-depressants (amitriptyline, relanium, etc) can be very effective in the elimination of the undesirable effects of these drugs. Thus, whilst the development of side effects (headaches, dizziness, flaccidity, dryness in the mouth, and urination disorders) were observed in 23 out of 39 patients (53.5%) with neuro-mental disorders of exogenous-organic genesis given increased doses of amitriptyline (from 50 to 75 mg), in Schizandra-treated patients a similar effect was observed in only 4 out of 172 patients (1.9%). Combined administration of tranquillisers and adaptogens permitted the usage of optimal doses of these drugs in 96% of patients, whilst it was only possible in 16% of control patients ($p < 0.001$) (Sudakov et. al. 1986).

From the reported findings it may be concluded that: (i) Schizandra extract can be used in psychiatric practice as a symptomatic agent against astheno-depressive states independent of the nature of the disease; (ii) preparations of Schizandra decrease drowsiness and flabbiness, improve the general mood and appetite, and can be recommended as a tonic for healthy people in a state of fatigue: no negative effects on the somatic state of patients have been observed; (iii) no changes in blood and urine have been observed following administration of Schizandra extract: the artherial blood pressure is normalised regardless if it was lower or higher than normal originally; (iv) in some cases, following use of Schizandra extract, acceleration and appearance of psychotic symptoms have been noted; (v) the duration of the Schizandra effect is different; (vi) the use of Schizandra therapy has no contraindication (exception high levels of heat); (vii) contraindications regarding mental state can be psychomotor excitement, a state of fear, anxiety, or agitated anguish, and prolonged hallucinative-delirious states; (viii) Schizandra extract can be used in the treatment of psychoses as a stimulant without harmful side effects; (ix) the curative effect of Schizandra preparations is pronounced in cases of asthenic and depressive syndromes; (x) the combination of Schizandra therapy with tranquillisers or anti-depressants eliminates the side effects of these drugs and allows them to be employed at optimal doses.

Conclusions and Perspectives of Implementation

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

Cramer and Spilker (1997) have suggested that the group of botanicals known as adaptogens could be useful in improving the quality of life for many categories of patients as well as for healthy subjects. It can also be anticipated that adaptogens will have a direct impact on many facets of physical health and psychological well-being, and may be indirectly important in a number of social and environmental areas. However, at the present time there is no clinical evidence concerning this matter: however, results from WHOQOL-100 and WHOQOL-BREF questionnaires may allow the formulation of evidence-based indications of adaptogens as remedies for the improvement in the quality of life, assessing the validity of the statement for adaptogens: ´one drug – many diseases‘.

Considering all of the above, we suggest that adaptogens will have not only specific therapeutic effects in some stress-induced and stress-related diseases, but will also have an impact on the quality of life of patients when implemented as adjuvants in the standard therapy of many chronic diseases and

pathological conditions (post-surgery recovery, asthenia, congestive heart failure, chronic obstructive pulmonary disease, type II diabetes, cancer, epilepsy, etc). However, numerous clinical trials will be required in order to provide evidence-based universal "over the counter" preparations which can be used by almost any patient in order to improve their general well-being and quality of life.

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