Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration

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Abstract

Plant adaptogens are compounds that increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors. The beneficial effects of multi-dose administration of adaptogens are mainly associated with the hypothalamic-pituitary-adrenal (HPA) axis, a part of the stress-system that is believed to play a primary role in the reactions of the body to repeated stress and adaptation. In contrast, the single dose application of adaptogens is important in situations that require a rapid response to tension or to a stressful situation. In this case, the effects of the adaptogens are associated with another part of the stress-system, namely, the sympatho-adrenal-system (SAS), that provides a rapid response mechanism mainly to control the acute reaction of the organism to a stressor. This review focuses primarily on the SAS-mediated stimulating effects of single doses of adaptogens derived from *Rhodiola rosea*, *Schizandra chinensis* and *Eleutherococcus senticosus*. The use of these drugs typically generates no side effects, unlike traditional stimulants that possess addiction, tolerance and abuse potential, produce a negative effect on sleep structure, and cause rebound hypersomnolence or "come down" effects. Furthermore, single administration of these adaptogens effectively increases mental performance and physical working capacity in humans. *R. rosea* is the most active of the three plant adaptogens producing, within 30 min of administration, a stimulating effect that continues for at least 4 -6 h. The active principles of the three plants that exhibit single dose stimulating effects are glycosides of phenylpropane- and phenylethane-based phenolic compounds such as salidroside, rosavin, syringin and triandrin, the latter being the most active.

Keywords: Adaptogens, Stimulating effect, Single dose effect, Clinical trials.

Introduction

Sensory adaptation is defined as the change in the excitability of a sense organ during continuous stimulation, the result of which is that increasingly intense stimuli are required to produce the same response. Physiological adaptation is defined as a biochemical change in an organism that results from exposure to certain environmental conditions or stressors and generates a more effective response to them. Such adaptive changes convey the organism from its normal steady state (homeostasis) to a heightened level of dynamic equilibrium (heterostasis) or to the so-called state of non-specific resistance (SNSR) (Lasarev, 1962; Brekhman and Dardymov, 1968) of the stress system (a function of the neuroendocrine-immune complex) (Chrousos and Gold, 1992). The general adaptation syndrome has three stages: the *alarm reaction*, being the point at which the body detects the external stimulus; *adaptation*, during which the body engages defensive countermeasures against the stressor; and *exhaustion,* where the body begins to run out of defences (Selye, 1950). Stress, including both *eustress* and *distress* (roughly meaning *challenge* and *overload*, respectively) may be the result of negative or positive events. Whilst eustress is essential to life (in the sense, for example, that exercise is required to avoid muscular atrophy), distress can cause disease. Eustress, however, raises the levels of adrenaline and prostaglandins in the body, which in turn increases the heart-rate, respiration, and blood-pressure and places greater physical stress on the body organs. Long-term stress can induce heart disease, high blood pressure, strokes and other illnesses (Chrousos et al., 1995; Fink, 2000).

In the mid 1900s it was suggested that SNSR could be achieved either by gradually training the organism to withstand the effect of the stressor, or by application of biological response modifiers i.e. chemicals that could directly raise the organism to a state of heterostasis. Such pharmacologically active compounds were given the name “adaptogens” (Lasarev, 1962). As originally defined, an adaptogen was a substance that: (a) showed some non-specific effect, such as increasing bodily resistance to physically, chemically, or biologically noxious agents or factors; (b) had a normalising influence on a pathologic state, independent of the nature of that state; and (c) was innocuous and did not disturb body functions at a normal level (Brekhman and Dardymov, 1968). More recently, plant adaptogens have been defined as compounds that increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors (Panossian et al., 1999a).

The repeated administration of adaptogens gives rise to an adaptogenic, or stress-protective, effect in a manner analogous to that produced by repeated physical exercise, leading to prolonged SNSR and increased endurance and stamina under extreme conditions (Dardymov, 1976; Lupandin and Lapajev, 1981; Viru, 1981; Saratikov and Krasnov, 2004). Such repeat doses of adaptogens have been shown to be of particular value in sports medicine in which the anti-fatigue effect can lead, for example, to the increased endurance of long distance runners during competition or to a more rapid recovery from a strenuous event (Korolevich and Lupandin, 1967; Levchenko, 1971; Lapajev, 1982; Lupandin, 1990; Bucci, 2000).

A characteristic feature of adaptogens is that they act as eustressors or challengers (Panossian et al., 1999b). Thus, a single administration of an adaptogen mainly produces a challenging (stimulating or stress-agonising) effect (Nörr, 1993; Panossian et al., 1999b, c; ESCOP Monographs, 2003a, b), a fact that is used in sports medicine where a single dose of adaptogen can increase the performance of sprinters by making them more alert (Astanin et al., 1943; Murtazin, 1946; Dalinger, 1966; Tuzov, 1968). It follows that the stress-protective effect achieved by multiple administration of adaptogens is not the result of inhibition of the stress response of an organism, but actually of adaptive changes in the organism as a response to the repeated stress-agonistic effect of the drug. In other words, using pharmacological terminology, adaptogens are stress-agonists and not stress-antagonists (Panossian et al., 1999b).

The beneficial effect of repeated treatment with adaptogens is mainly evident in patients suffering from chronic disease or a disturbed state (Krasik et al., 1970a, b; Lebedev, 1971; Lapajev, 1978; Lupandin and Lapajev, 1981; Mikhailova, 1983; Panossian et al., 1997; ESCOP Monographs, 2003a, b; Saratikov and Krasnov, 2004). Such effects are mainly associated with the hypothalamic-pituitary-adrenal (HPA) axis, a part of the stress system that is believed to play a primary role in the reactions of the body to repeated stress and to adaptation by balancing the releases of adrenaline (the "switch-on" hormone), corticosteroids (the feed-back regulatory "switch off" hormones that protect an organism from overreaction), and nitric oxide (that modulates the biosynthesis and effects of many hormones and autacoids, and plays a role in the nervous, cardiovascular, immune, gastrointestinal and endocrine systems).

In contrast, the application of adaptogens in a single dose is important in situations that require a rapid response to strain or to a stressful situation. In such cases, the effects are associated with another part of the stress-system, namely, the sympatho-adrenal-system (SAS) . This system provides a rapid response mechanism that mainly controls the acute response of the organism to a stressor, resulting in increased levels of catecholamines, neuropeptides, ATP, nitric oxide and eicosanoids. The present review will focus primarily on the characteristic SAS-stimulating effects of the plant adaptogens.

The stimulating effect of adaptogens

The earliest studies of adaptogens (*cf.* Table 1) were concerned primarily with demonstrating their ability to increase the mental and physical working capacity in humans (Medvedev, 1963; Dalinger, 1966; Tuzov, 1968) and in animals following administration of single or repeated doses (Lebedev, 1971; Lapajev, 1978; Lupandin and Lapajev, 1981; Panossian et al., 1997; ESCOP Monographs, 2003a, b; Saratikov and Krasnov, 2004). It soon became clear, however, that there were very important differences between the stimulating effects of adaptogens and those of other stimulants of the CNS and these are summarised in Table 2 (Fulder, 1980) .

Stimulants, defined as drugs that increase the activity of the sympathetic nervous system, produce a sense of euphoria and can be used to increase alertness and the ability to concentrate on mental tasks. Stimulants such as caffeine, nicotine, amphetamines and cocaine, are also used, and sometimes abused, to boost endurance and productivity. However, long-term stimulant abuse can impair mental function and lead to psychotic symptoms. Furthermore, traditional stimulants that possess addiction, tolerance and abuse potential, produce a negative effect on sleep structure, and cause rebound hypersomnolence or "come down" effects. By definition, plant adaptogens do not exhibit such negative effects: in fact one plant adaptogen, that derived from *Rhodiola rosea*, has been shown significantly to regulate high-altitude sleep disorders and to improve sleep quality (Ha et al., 2002).

Plant adaptogens stimulate the nervous system by mechanisms that are totally different from those of traditional stimulants, being associated rather with metabolic regulation of various elements of the stress-system and modulation of stimulus-response coupling (Petkov, 1978; Bombardelli et al., 1980; Hasan Samira et al., 1985; Wagner et al., 1994; Panossian et al., 1999b; Panossian, 2003). Depending on the mediators of the stress-system involved in the adaptogen-induced stress-response, an immediate (single dose effect) or a long term (after multiple administration) stimulating effect may be observed. Whilst the efficacy of repeated administration of adaptogens at improving mental performance over various time periods is well documented (Darbinyan et al., 2000; Spasov et al., 2000a, b), reports on single dose effects are fragmentary and have yet to be given comprehensive consideration. This article reviews the results that have been recorded in human subjects and, to a lesser extent, in laboratory animals following single treatment with plant adaptogens.

Studies involving animal models

It has been shown that small doses of an extract of *R. rosea*, or of its active ingredient salidroside (**1**), increases the spontaneous bio-electrical activity of the brains of test animals, 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). Unlike tranquillisers, however, medium range doses of the adaptogen enhance the development of conditioned avoidance reflexes in rats, and facilitate learning based on positive reinforcement (Saratikov et al., 1965). In a staircase experiment, involving a device consisting of 13 steps and four feeders, rats were starved for 23 h and then trained to climb to the 12th step in order to receive their food ration: one training session was carried out with each animal for five successive days and the criterion for learning was the number of trained animals recorded on day 5 (Petkov et al., 1986). With positive (food) reinforcement, single administration of an extract of *R. rosea* (0.1 mL per animal) produced a significant increase in the number of trained animals (Fig. 1). In passive avoidance tests, however, no significant differences were recorded between the control animals and those treated with multiple administrations for up to 10 days. The results obtained clearly depended on the test methods employed and the differences noted could indicate different neurochemical mechanisms underlying the training methods.

In a maze test with negative (punitive) reinforcement, significant enhancements in learning and retention were detected in rats following the single dose application of an extract of *R. rosea* at a rate of 0.1 mL per animal (Petkov et al., 1986). The experiments were carried out using a multi-chamber, semi-automatic maze: a quiet buzzer was used as the conditional signal, followed by punitive reinforcement in the form of a small electrical current on the floor grid that was maintained until the rat entered the goal section of the maze.. Training was performed in one session until the test animal had found its way to the goal-section in six successive attempts. Retention parameters were considered to be the number of correct responses (entry of the test animal into the goal-section) and their latencies 24 h after training, and these parameters improved significantly following treatment with the plant adaptogen (Figs. 2 and 3). Repeated administration of the drug at the same dose level showed similar effects.

Extracts of *R. rosea* have been reported to exhibit interesting dose-dependant effects on the duration of thiopental-induced sleep in mice (Fig. 4), ranging from stimulation at low doses (10 mg/kg) doses, where the sleep period was reduced by 12.5 times, to sedation at high doses (500 mg/kg), where the sleep period was increased 3-fold (Kurkin et al., 2003).

Ten days after oral administration of an aqueous extract of *R. rosea*, the levels of norepinephrine (NE), dopamine (DA) and serotonin (5-HT) in the brainstem of the experimental animals increased considerably compared with 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 with 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 has been suggested (Saratikov et. al. 1965, 1978; Marina 1968; Marina and Alekseeva 1968; Saratikov and Krasnov 2004; Kurkin and Zapesochnaya 1986), 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.

Using animal models, bioassay-guided fractionation of various extracts of plant adaptogens have shown that the active principles are mainly phenylpropane and phenylethane derivatives including salidroside (**1**), rosavin (**2**), syringin (**3**), triandrin (**4**), tyrosol (**5**), etc (Lebedev, 1951a, 1967; Aksenova, 1969; Aksenova et al., 1968 ; Dardymov, 1976; Kurkin and Zapesochnaya, 1986; Nishibe et al., 1990; Zapesochnaya et al., 1995; Saratikov and Krasnov, 2004). Of these, **1** was reported to be the most active in a number of different test systems (Figs. 5 and 6; Barnaulov et al., 1986). However, in a more recent comparative study, it has been demonstrated that **4** exhibited the largest stimulating effect after a single oral administration (Figs. 7 – 9; Sokolov et al., 1990, Zapesochnaya et al., 1995) and also showed the highest bioavailability (Zapesochnaya et al., 1995). Moreover, whilst nearly all of the 27 pure compounds isolated from *R. sachalinensis* (including **1** and **2**) screened against propyl endoperoxidase (which is known to play a role in the degradation of proline-containing neuropeptides involved in the process of learning and memory) showed inhibitory activity, the most potent was 1,2,3,6-tetragogouyl-glucose (Fan et al., 2001).

Studies involving human subjects

The results of such studies are summarised in Table 1 in which the type and level of evidence gathered has been classified according to the WHO, FDA and EMEA systems. The most important effects reported were increases in: (i) mental working capacity, (ii) physical working capacity, (iii) the accuracy of movement, and (iv) the visual functions of the eye.

Effect of adaptogens on mental working capacity

The effect of a single dose of an extract of *R. rosea* on the mental performance of 85 healthy males and females, in the age range 20 – 28 years old and working under the same conditions, was studied by Zotova (1965) using Anfimov's table, which provides the possibility of obtaining numerically comparable data characterising the quality and quantity of work performed. The subjects were asked to cross through letters A and C in a text within a fixed time of 5 min. Subjects were grouped, and each group was treated separately with different doses of *R. rosea* extract and finally with placebo (coloured, 40 % aqueous alcohol): in this manner, any possible improvement in the results occasioned by learning how to perform the test were eliminated. Each subject performed the task twice, once before treatment with the extract/placebo and a second time 1 h after the treatment. The results indicated that, compared to treatment with the placebo, application of *R. rosea* extract did not affect the quantity of characters correctly crossed through, but considerably reduced the number of errors made. Doses of 5-10 drops were found to be the most effective, reducing the number of errors by an average of 46% (Fig. 10a). At a dose of 5 drops, the treatment with the extract lead to a reduction in the number of errors in 88% of the subjects tested, but to an increase in the remaining 12%. Application of the placebo produced a reduction in the number of errors in 35% of the subjects, an increase in 58% and no change in the remaining 7%. (Fig. 10b). It was found that at a dose of 7 drops, the extract exhibited a pronounced stimulating effect that lasted some 4 h or longer (Zotova, 1965). In a complementary study, the effect of salidroside (**1**) alone was shown to be highly comparable with that of the extract of *R. rosea* (*cf.* Fig. 10) (Aksenova et al., 1968).

A similar study protocol was employed by Komar et al. (1981) in order to compare the effects of preparations of *R. rosea* and *Eleutherococcus senticosus* on human mental activity. In this work, 254 men and women were treated with an adaptogen extract or with a tincture of *Mentha* as the control. The *R. rosea* extract was more active than that of *E.*

senticosus in terms of increasing working capacity (the difference in the number of corrected symbols), efficacy (performance, decreasing the number of errors) and speed of information processing and perception. Unfortunately, it was not stated if the trial was randomised and blind, or if the differences between the results of the verum and control groups were statistically significant. From a separate series of tests conducted up to 8 h after administration of the *R. rosea* extract, the same authors claimed that the stimulating effect lasted for at least 4 h, but again the statistical status of the significance of these results remains unknown.

In another study involving text correction using Anfimov's tables and the ability to memorise paragraphs of text, 82 volunteers were treated with either 5 drops of extract of *R. rosea* or a dose (1, 5, 10 or 20 mg) of pure tyrosol (**5**; an active component of *R. rosea*) (Marina et al., 1994). The mental working capacities of the subjects were evaluated after treatment, and it was demonstrated that whilst neither preparation produced an effect on the time taken to perform the correction task, both improved the quality of performance, reducing the percentage of errors by 29-35% compared with the control, and increasing the volume of the short-term memory as represented by the number of text paragraphs recalled. The differences between the results of groups taking different doses of **5** and of the extract were not statistically significant (Marina et al., 1994).

More recently, a randomised, double-blind, placebo-controlled parallel group clinical study with an extra non-treatment control group was performed (Shevtsov et al., 2003) in order to measure the effect of a single dose (of 2 or 3 capsules) of a standardised extract of *R. rosea* (SHR-5; 180 mg per gelatine capsule) on the capacity for mental (psychometric tests) work against a background of fatigue and stress. The analysis, which involved 161 cadets, demonstrated that both doses of the extract produced statistically significant ($p<0.001$) anti-fatigue (stimulating) effects, together with similarly significant beneficial effects on pulse pressure, compared with the placebo.

In 1988, Grigorenko and Berdyshev, reported that a single daily dose of *S. chinensis* tea produced, for at least the first 7 - 10 days of treatment, a tonic effect in sailors who were keeping watch. After 2 - 3 weeks of continuous use of the tea, some subjects developed sleeplessness, excitability and a low level of general well-being, although these negative side effects could be eliminated by interludes with black tea. In an extension to this work, a systematic placebo-controlled cross over study of various aspects of single dose administration of both *E. senticosus* and *S. chinensis* on the mental performance of 357 sailors on watch duty was performed (Berdyshev, 1995). Subjects took different doses of the preparations prior to their watch period and, 30 – 60 min before such administration, a correction test was used to evaluate mental performance. A similar correction test was conducted immediately (30 – 60 min) after the watch, and subjects were further tested before and after watch duty every 4 - 5 days in order to exclude a possible cumulative effect of the treatment.

Single doses of between 0.25 and 8 mL of *E. senticosus* extract were administered to sailors before the watch, and a dose of 4 ml was found to be the most effective in improving working ability. Doses of up to 1 mL did not have the desired effect on most of the subjects, whilst doses of larger than 4 mL did not improve the results in the test group. At a dose of 8 mL, only 49% of subjects showed a positive effect and, moreover, the subjective condition and several objective parameters of some subjects in this group (11 out of 62) became worse i.e. for a short period (20 - 40 min) the subjects felt sleepy and flabby, whilst the indirect parameters associated with their working ability and blood pressure decreased. In order to study the daily dynamics of the effect of a single 4 mL dose of *E. senticosus* extract, additional studies were carried out involving 72 of the original sailors carrying out similar tasks inside the ship whilst on different watches. The considerable differences revealed in the efficacy of *E. senticosus* were found to be related to the individual typological features of the subject, including daily and seasonal biorhythms. In the morning, positive effects on working ability occasioned by the adaptogen were most pronounced in subjects presenting the morning type of biorhythmic activity (83% of the subjects) compared with only 39% of the subjects exhibiting the evening type of activity. In the evening, the results were quite different in that the adaptogen showed much better results in subjects with the evening type of biorhythmic activity. At night, when the overall effect of the preparation was relatively low, the correlation with biorhythmic type practically disappeared.

In order to determine if the efficacy of the extract of *E. senticosus* was associated with the functional state of the organism, a correlation analysis was carried out on the same group of sailors with respect to the initial (before work) values of various biochemical parameters (Table 3). For sailors working on all watches, positive relationships between the efficacy of the adaptogen and the activity of the adrenal cortex (excretion of 17-ketosteroids in the urine), the activity of the sympathetic adrenomedullar system (orthostatic test), the intensity of metabolic processes (excretion of vitamin C in the urine), and the intensity of oxidation-reduction processes (Rotter test) could be demonstrated. In contrast, the activity of the parasympathetic nervous system (clinostatic test), non-specific resistance (percentage phagocytosis, phagocytic index, vascular resistance, and osmotic resistance of erythrocytes) and the endurance to hypoxia (Hench test with retention of breathing at exhalation) all showed negative correlations with efficacy of the drug.

In a similar, comparative analysis (Berdyshev, 1995), 44 sailors (whose duties involved hard work under severe winter conditions) were administered placebo, 4 mL of *E. senticosus* extract, or 3 mL of *S. chinensis* tincture, each on a separate test day, and then examined before and after completing their watches. Using a paired correlation method, the relationship between the effect of the adaptogens (determined individually according to the working ability of the subject) and the differences in functional changes during the watch (compared with the placebo values for that subject) were calculated for each sailor (Table 4). On the basis of these results, the author suggested that in subjects working under stress the effect of a single dose of *E. senticosus* was occasioned by a pronounced increase in the tonus of the parasympathetic part of the autonomic nervous system, a moderate intensification of excitation of the CNS and of energy metabolism with practically unchanged respiratory coefficient, a tendency towards the intensification of oxidation-reduction processes in tissues, improvement of cortical processes and balance, and in cardiovascular system activity thanks to slower pulse and increased pulse pressure, a decrease in adrenal cortex activity, catabolic processes, and the tonus of the sympathetic part of the autonomic nervous system, and a reduction in the increase of body temperature. It was concluded that the increase in working ability following treatment with the adaptogen was associated with improved endurance to hypoxia and improvement in the parameters of non-specific resistance of the subject. Furthermore, treatment with an extract of *E. senticosus* was claimed to reduce excessive exertion of the organism by virtue of its effect on adrenal function and tonus of the autonomic nervous system.

On the other hand, the results of the correlation analysis suggested that the increase in work capacity induced by a single dose of *S. chinensis* was brought about by a quite different mechanism. Thus, improvement in mental performance correlated positively with increased energy metabolism and catabolic processes, increased tonus of the CNS, and intensified activities of the sympathetic adrenomedullar, the adrenal and the cardiovascular systems. This, in turn, coincided with an increase in body temperature, a lowered endurance to hypoxia, and a decrease in some parameters of non-specific resistance of the subject. These facts indicate that the effects of this adaptogen are associated with the additional mobilisation of energy resources, i.e. *S. chinensis* is, evidently, a mild stimulant.

The differences in the effects produced by *E. senticosus* and by *S. chinensis* on working ability and function of subjects at night time can be explained in terms of the differences in mechanism of action of the two drugs. Table 5 shows the levels of various functional parameters determined in groups of sailors after performing their duties under conditions of high temperature and humidity between the hours of midnight and 4 am (Berdyshev, 1995). The subjects were administered either a placebo or one of the test drugs directly before their watch, and were examined immediately after having performed their duty (between 4 and 5 am). The results show that, in contrast to *E. senticosus,* treatment with *S. chinensis* stimulated the activity of the CNS at night (activated excitation processes and normalised nervous processes ratio), increased tonus of the sympathetic part of the autonomic nervous system (having no effect on the parasympathetic part), activated the adrenal cortex activity, increased the activity of the cardiovascular and respiratory systems, intensified oxidation-reduction and metabolic processes, improved working ability parameters and, at the same time, reduced parameters of non-specific resistance the organism and cellular structure resistance and increased body temperature (Berdyshev, 1995).

Differences in the stimulating effects of various adaptogens following single administration were demonstrated by Medvedev (1963) in a study involving radio operators. It was shown that, compared with placebo, an extract of *E. senticosus* significantly decreased the number of errors in messages transmitted by tired operators. The stimulating effect of *E. senticosus* was strong and stable whilst that produced by *Panax ginseng* was insignificant (Fig. 11)

A series of in-depth studies have been carried out at the Centre for Space Medicine of the Institute of Medicinal and Biological Problems (IMBD) and at the Moscow Aviation

Institute (Bogatova and Malozemov, 1994; Bogatova et al., 1997) in order to evaluate the effect of a fixed and standardised combination of extracts of *S. chinensis, E. senticosus* and *R. rosea* [ADAPT-232; capsules containing 3 mg of salidroside (**1**), 4 mg of schizandrin (**6**), and 3 mg eleutheroside B (**7**)]. The consequence on short-term memory, power of comprehension, and oculomotor co-ordination in five Russian cosmonauts treated with a single dose of ADAPT-232 during their training in prolonged isolation (90 days) under conditions of long-term, monotonous work was evaluated in a placebo controlled pilot study. Computer-generated psychometric tests were carried out at various times after treatment of the subjects and the results demonstrated that, within 4 h of application, ADAPT-232 significantly decreased the number of mistakes in complicated psychometric tests but had no significant effect in non-complicated tests.

In a follow-up study, 60 volunteers, selected from a population of 97 on the basis of high results ($\geq$ 7.5 out of 10) in a psychometric test, were divided into 6 equal groups and each group was tested against itself after taking ADAPT-232 (3 capsules once a day) or placebo according to a crossover design with a wash-out period of 3 days. The study consisted of three sections: (i) examination of mental performance during 24 h continuous work after a single-dose treatment, (ii) examination of the mental and physical (mainly cardiovascular) work capacity against a background of fatigue or/and stress during repeated-dose treatment, and (iii) assessment of the well-being of treated subjects as determined from their subjective view of the level of difficulty of the tests applied. The main aim of the study was to determine the effect of adaptogens during monotonous and long-term work under conditions that simulated the environment on the space stations SaIjut and Mir. For this purpose a highly sophisticated computer-based test (Monotonic 2) was employed, which consisted of a well-tried and validated battery of assessments measuring mental performance during space-like conditions.

Monotonic 2 was developed and refined over a period of 20 years and has proven to be much more reliable than standard tests with pencil and paper. The most important parameters assessed are speed, reliability and the ability to comprehend, learn and reproduce new information with high precision during monotonous and long working shifts. In order to study the dynamics of a single dose effect, as well as the on-set of an effect, each subject performed 18 h of monotonous work and then had to respond to the computer program continuously during the test (which started at 2 am). Scores representing (i) speed and reliability in the understanding of information (t), and (ii) precision and accuracy in the ability to reproduce the information (h), were recorded every 30 min for each subject. The lower the value of t, the higher the speed; the higher the value of h, the higher the precision: taken together, the values of t and h also provided an indicator of the level of tiredness and concentration in repeated tests. The results of the Monotonic 2 test concerning mental work capacity are shown in Fig.12 in which the mean data for each group are displayed. Regarding the on-set of the effect, tests revealed a significant increase in performance after 1 – 2 h.. With respect to the parameters of speed and precision, an increase in mental work capacity after intake of ADAPT-232 is clearly seen in Fig. 12 from the difference in area between the two curves.

An alternative fixed and standardised combination of extracts of *S. chinensis, E. senticosus* and *R. rosea* (Rodelim) has also been shown to increase significantly the mental working capacity of healthy volunteers when applied in repeated or single-dose format (Vezirishvili et al., 1999; Roslyakova et al., 2000). The assessment was based on a study of the psycho-emotional and psycho-physiological states, the professional and mental working capacity, and the cardiovascular system of 60 computer operators on night duty under conditions that simulated long monotonous activity inducing fatigue. The methods of evaluation included mathematical analysis of the cardiac rhythm, computer tests, questionnaires and psycho-physiological tests, ophthalmologic examinations, and medical tests (heart rate, ECG and respiration parameters, blood pressure, etc).

The effects of powdered seeds of *S. chinensis* on the mental working capacity of 59 students was studied (Lebedev, 1951a, b; Kochmareva, 1958) using a method of text correction in which fatigue decreased the accuracy but not the speed of work. Following treatment, the performance of 38 subjects (65%) improved, 17 showing an increase in the number and quality of corrections made, 14 demonstrating an improvement only in quality of correction, and 7 an increase only in the amount of work performed. Six constituents were isolated from the seed material and the tests repeated on 20 subjects, every one of whom received each of the compounds individually. Schizandrin (**6**) was found to be the most active substance present in the seed material. A dose of 3.6 mg of **6** prevented exhaustion-related errors in text correction by the subjects: errors of the control group (treated with placebo) amounted to 228% whilst those of the treated group were only 95% (errors in the control test normalised to 100%) (Lebedev, 1951 a,b, 1967).

In another study, involving telegraph operators between the ages of 21 and 24 years, the same author showed that single doses of either an extract of *S. chinensis* (30 mL;10% in 70% aqueous ethanol) or of compound **6** (5, 10 and 20 mg) prevented exhaustion-related errors in transmitting Morse code at maximum speed for 5 min (Lebedev, 1967). In this duplicated set of experiments ($n_1 = 20$, $n_2 = 23$) the frequency of errors made by the control groups (given glucose or 70% aqueous ethanol as placebo) was 130%, whilst the error frequency of the treated groups was 84 - 103% (errors in the control test normalised to 100%). Similar results were obtained following treatment of the operators with *P. ginseng* or with phenamine: however, the latter produced an effect of excitation that increased speed but not performance.

Along with the demonstration that adaptogens could improve mental capacity of healthy subjects, a number of Russian researchers conceived the idea that they could be used for a treatment of some neurotic conditions. Kaliko and Tarasova (1966) studied the effects of extracts of *R. rosea* and *Rhaponticum cartamoides* on 80 healthy students and 70 neurotic patients employing the so-called Ivanov-Smolenski verbal experiment with speech-supported locomotor-conditioned reflex measurement. In this test, 25 words conveying exciting images were located in sequence with words requiring a reflective oral response from the subject. Excitation was assessed by the speed of formation, stability and intensity of reflex movements, whilst calming effects were determined from the latent period between a questioning word and the response, and also from the character of the response. The verbal experiment was performed twice (using a different set of 25 words on each occasion) with each participant, once before drug administration and once following a single or repeated dose of the extract. It was found that, in single dose form, neither extract induced an effect on the functioning of the CNS in healthy subjects. However, in patients with neurosis, a single dose of *Rhodiola rosea* extract brought about significant changes in the functional state of the CNS as characterised by normalisation of the speed and the power of neural processes. The latent period of speech reflex decreased to between 1 and 3 s (1.6 s was accepted as the normal latent period of speech response), and stereotype answers and refusals disappeared. Conditioned reflexes were formed at the first associations, their latent period decreased, the size of the reflexes increased, generalised reactions disappeared, transformation of positive-conditioned irritants into negative ones arose after the first associations, the memory improved, and passive and (particularly) active attention became more stable**.** Repeat testing 3 days after single dose administration showed that the described improvement in functioning of the CNS was only temporary (Kaliko and Tarasova, 1966). However, a more stable effect was achieved by multiple administration of extracts of *R. rosea* and *Rhaponticum cartamoides* over a 10 day period.

Effect of adaptogens on physical working capacity

Not only can the administration of plant adaptogens improve mental performance, they can also stimulate the brain cortex and thus increase physical capacity as well. The working capacity and physical force of men using the Dubua ergographic test was increased by 24 – 42% (*cf.* control) after 1 - 3 h following administration of a single dose of a 70% ethanolic extract of the seeds of *S. chinensis* (Karo, 1945; Lazarev, 1946): aqueous extracts of seeds and extracts of berries, however, showed no such activity. Following treatment with capsules containing the powdered seeds of *S. chinensis*, the stimulatory effect was observable within 2 – 2.5 h, reached a maximum at 3.5 h and had disappeared after 5.5 h (Kokhanova et al., 1950). Subjects who had been fatigued by sawing wood for 5 min (at a frequency of 45 saw movements/min) prior to treatment with *S. chinensis* exhibited a more pronounced enhancement of their working capacity (as measured by the Dubua test), which increased from 27.5 kg/m in the control group to 77 kg/m in the treated group.

Studies carried out using the classical ergometric bicycle (60 kg load), in which the number of revolutions completed by the subject was counted up to the point of exhaustion, revealed an even greater stimulatory effect of *S. chinensis.* Yefimova et al. (1954) reported that healthy subjects showed a more than 2-fold increase in working capacity following administration of a single dose of seed powder, whilst students tested using similar methods exhibited an increase in working capacity from 620 kg/m (mean control value for placebo group) to 1736 kg/m. The classical ergographic procedure was also used by Andrejev and Georgijev (1958) who observed a 49.2% increase in the working capacity of healthy subjects.

In athletes and rowers, a 20% tincture of *S. chinensis* seed, administered in doses of 2, 5, 10 or 15 g and applied 1, 2 or 3 h before physical exercise, improved the function of the respiratory and cardio-vascular systems, increased muscle power of the hand muscles, and reduced the time required by the athletes to complete the course (Eglit et al., 1965): the improvements appeared to be particularly significant for groups of canoeists treated with the tincture 1 h before single-handed races.

Powdered seed material of *S. chinensis* supplied in capsule form to Red Army soldiers before they undertook a 20 km ski run, reduced exhaustion and shortage of breath, the feeling of thirst and dryness of the mouth, and muscular pain compared with a control group who had been given a placebo capsule (Murtazin, 1946). The treated soldiers were able to complete the run in a shorter time than the control group, and similar sets of results were recorded for treated and control groups of civilian skiers tested under the same conditions.

Results recorded for runners treated with preparations of *S. chinensis* appear a little more complex, however. Application of a tincture of *S. chinensis* produced a negative effect on the times taken for runners to complete a 100 m course, but when the same subjects were required to complete the longer distance of 1000 m, some 60% of the runners showed significantly improved times, and the overall average improvement for all runners was 4.45 s (Astanin et al., 1943). After receiving ethanol or caffeine, the times taken by these runners to complete 1000 m were longer than those recorded in preliminary runs (before which they had received no treatment), and considerably longer than the times recorded after receiving *S. chinensis* or amphetamine. In corroboration of these positive responses, Lebedev (1967, 1971) reported that schizandrin (**6**: an active component of *S. chinensis*) increased the working capacities of 20 year-old runners performing over a distance of 3000 m such that their running times were remarkably shorter than those of a control group that had been treated with placebo (glucose). In all doses tested, the stimulating effect of **6** was of the same order of magnitude as that of phenamine.

A very detailed report is available concerning the effects of *E. senticosus* on the activity of the cardio-vascular system and the capacity for work of skiers. In this study (Dalinger, 1966), groups of sportsmen took part in one of a number of different events, i.e. ski races of 20, 30 or 40 km, or a biathlon (a 20 km ski run carrying a rifle and involving target shooting at various locations during the race), or a 6-day ski hike over 150 km whilst carrying kit: each event was held under severe conditions (air temperature of -28 to –23°C with a strong wind). Within each group, half were given an alcoholic extract of *E. senticosus* and the other half an infusion of tea with a small amount of alcohol: both preparations looked and tasted the same, and the skiers did not know which they had been given. Before commencing the competition, subjects underwent several tests including a combined Letunov's functional test, oxyhemography with a functional test in the form of a dosed delay of respiration for 50 s and a test with a maximum delay of respiration (Stange's test), whilst the muscular tonus of the biceps and triceps brachia, and the quadrate muscle of the thigh and the gastrocnemius was measured by means of a myotonometer (Searman's system). The tests were repeated immediately after completion of the event, during the first 30 min and during the recovery period, and 6 h, 1 and 2 days later. The short-distance skiers were given their preparation in the form of a single dose (4 mL) some 90, 60 or 45 min before the start of the event: the long-distance skiers were given daily doses (2 mL each) of preparation, the first administration being 6 h after starting the event, with a final dose (4 mL) on the last day of the hike.

Generally, those subjects who had received extract of *E. senticosus* showed an increase in the capacity for work (with easier breathing on the track), undertook the ascents with greater energy, did not feel fatigue after the extended work, noted a pronounced feeling of muscular vigour, slept well, enjoyed a good appetite, and were happy to return to training after completion of the event. The athletes who had received the placebo showed no such positive changes. The Letunov's functional test indicated that, in most cases, increases in pulse rate and arterial pressure were less pronounced in treated skiers in comparison with the appropriate control group, and the elevated levels returned to normal sooner (within 30 – 40 min rather than 80 min as recorded for the control group). When subjected to Stange's test (at sub-maximal respiration) 30 min after the event, athletes treated with *E. senticosus* presented an average value of 110.8 s whilst the average value for those given placebo was 103.9 s, indicating a higher functional status of the cardio-vascular and nervous system in the treated group. The oxyhemographic study indicated that the adaptogen increased the athletes' steadiness and resistance to hypoxemia. The results of the delayed breathing test in combination with oxyhemography, indicated an increase in resistance to oxygen insufficiency in skiers who had taken the *E. senticosus* extract, together with a more rapid restoration of blood oxygenation after dosed delayed respiration and after maximum delay of breathing.

An indication of the powerful restoring effect of the adaptogen was demonstrated by its influence on muscular tonus. After taking the preparation, skiers found that it became easier to perform heavy muscular work and the residual muscular tonus was less pronounced. After 24 h there were practically no manifestations of residual tonus in the treated skiers whereas in the athletes of the control group the residual tonus still was somewhat pronounced. The decrease of the residual tonus below initial values suggests that extracts of *E. senticosus* stimulate a more active recovery following heavy physical loading (Dalinger, 1966).

No difference was observed between the control and the treated groups with respect to the average time taken to cover the distance in the 20 km race but, of the expert skiers who took part in the 30 km race, those treated with *E. senticosus* extract produced significantly faster times than members of the placebo group. In the biathlon, the treated group scored a significantly higher number of target hits in the shooting event compared with the control group (14 *versus* 10, respectively). Within the groups who had participated in the 6-day hike, those receiving the verum claimed that they had not felt any fatigue but had experienced a rapid restoration of strength shortly after taking the preparation. The restoration of pulse and arterial pressure to the initial levels proceeded twice as rapidly (towards the end of the first 24 h) in the treated group compared with the control group (delayed typically to the third day).

Tuzov (1968) conducted a placebo-controlled, randomised, single blind comparative study of the effects of *E. senticosus, Rhodiola rosea, Rhaponticum cartamoides* and *Panax ginseng* on the muscular working capacities of 52 healthy athletes (aged between 18 and 24 years) who were exposed to various physical loads. Experiments were performed either in the absence or presence of background fatigue, and the amount and intensity of work performed was evaluated. In the first set of experiments the study drug or the placebo solution was administered to a subject who then rested for 30 min before operating the bicycle in sprint mode (maximum race speed) for 30 s. After a 5 min rest the subject repeated the task, during which time the resistance to rotation of the wheels was adjusted to suit the functional abilities of the athlete. The aim of this procedure was to ensure that each subject would be able to carry out continuous work at the highest load intensity for a duration of 20 – 30 min before exhaustion set in. The exact time taken for each subject to reach exhaustion after working at their appropriately chosen pace was recorded, together with the determined amount and intensity of work performed during that period .

In a second series of experiments in which the subjects were in a state of fatigue before measurements were made, the drug or placebo was administered and, rather than resting for 30 min, athletes were asked to carry out standard dosed work for 25 min followed by a 5 min rest before the prescribed 30 s sprints and timed exercise began. Tests were repeated at intervals of 2 – 3 days, and on each occasion subjects received 15 drops of *Rhodiola rosea* extract, or 2 mL of an extract of *E. senticosus, Rhaponticum cartamoides* or

P. ginseng, or an equivalent volume of placebo with similar organoleptic properties. The subjects had no knowledge of the nature of the drug administered on any particular occasion: in fact, application of adaptogens commenced only after a period of adaptation to physical load when the subject had got used to working on the training equipment and the values of the intensity of muscular work became relatively uniform. The results showed that the efficacy of the drug depended on the duration of the physical loading and the background fatigue of the subject. Thus, in the absence of prior fatigue, adaptogens showed no effect on the intensity of the sprint work. However, when the subjects were pre-fatigued, the maximum intensity of the sprint was increased moderately (9% *versus.* placebo) but significantly ($p<0.05$) by application of the extract of *Rhodiola rosea* but not by the other extracts (Fig. 13a). In contrast, under physical loading using a preset high-intensity test, all studied adaptogens showed statistically significant stimulating effects (Fig.13b) except for that derived from *P. ginseng*. The best results were obtained with the extract of *R. rosea* that, on pre-fatigued subjects, lead to a prolongation of work by about 28% compared with the placebo (Tuzov, 1968). With pre-fatigued athletes, improvements in the general state and functional indices, as well as a reduction in the recovery period, were observed in all subjects taking herbal stimulants. Furthermore, an improvement in the response of the blood circulation system to physical load, presumably caused by an increase in the stroke volume, was also observed in all athletes who had been given the herbal stimulants. The largest improvements in pulse rate and the highest blood pressure values were observed in subjects who had been treated with *Rhodiola rosea*. The adaptogens also showed a positive effect on the muscular force of the back and of the hand muscles as determined by spirometry (Tuzov, 1968).

In a recent double-blind placebo controlled randomised study of the effects of acute and 4-week intake of a standardised extract of *R. rosea* on the physical capacity, muscular strength, speed of limb movement, reaction time and attention in young volunteers, it was demonstrated that treatment improved endurance in exercise performance (De Bock et al., 2004). Compared with the placebo group, acute intake of *R. rosea* extract increased the time to exhaustion slightly but significantly; however, daily intake of the drug for 4 weeks produced no significant difference compared with placebo treatment. These results contrast with several other studies where significant effects on mental and physical performance following repeated administration of *R. rosea* extract have been observed (Darbinyan et al., 2000; Spasov et al., 2000a, b)

Very recently, a study involving a commercial, herbal-based formula containing root of *R. rosea* appeared to demonstrate that the preparation did not elicit positive changes in cycling performance (Earnest et al., 2004). The discrepancy of the results from this study compared with the numerous other studies require explanation. It might simply be that the batch of the drug employed was not analysed prior to the experiment in order to ensure compliance with specification. As an example of the necessity of such control, it should be mentioned that in a systematic study of 25 commercial samples of Ginseng and Eleutherococcus obtained from a local health food store, the concentrations of active ingredients varied by 15- and 400-fold (Harkey et al., 2001).

Effect of adaptogens on the visual functions of eye

Increases in the peripheral sensitivity of the retina have been reported (Galochkina, 1948) after administration of a single dose of the air-dried powder of fruits of *S. chinensis* (mixed with starch and glucose) followed by 50 – 60 min of adaptation to darkness. This treatment also increased sensitivity to red light (600 nm) but decreased sensitivity to green light (520 nm), an outcome that is possibly associated with a parasympathomimetic effect of drug.

In a related placebo-controlled study involving healthy subjects (Trusov, 1953), the single administration of capsules containing 3 g of *S. chinensis* seed powder was shown to enhance night vision and to accelerate adaptation to darkness. For each individual, sensitivity to light and acuity of vision, and visual field margins of colours were measured, respectively, 1.5 and 3 h after drug administration, and the results compared with those obtained in an initial evaluation of visual function carried out 10 – 15 min before treatment. It was clearly demonstrated that *S. chinensis* increased visual acuity under low illumination and extended the visual field margins for white and red light by 8 to 25°. A later extension of this work (Trusov, 1958a, b) employed two further scales for the measurement of visual sensitivity, namely, the time taken to recognise an object in darkness, and the maximum level of darkness that permitted such object recognition (an evaluation of adaptation to darkness). Ninety percent of healthy subjects who received a single dose (3 g) of *S. chinensis* seed powder showed significantly increased visual sensitivity. Some 4.5 h after application of the adaptogen, the time required for visual recognition of an object in darkness had decreased from 32.3 to 18.4 s and adaptation to darkness had improved markedly.

Since *S. chinensis* increased the rate of increase of visual sensitivity, but not the final level of sensitivity, it was concluded that the adaptogen affects the neural mechanisms of adaptation to darkness rather than the photochemical processes in the retina of the aye. (Trusov, 1958 a, b). This same study also provided some indication of the mode of action of *S. chinensis,* since pharmacological agents that mainly affect the brain cortex are known to induce equal changes in visual sensitivity in all regions of the visible spectrum, whilst agents that act on the vegetative nervous system and/or the hypothalamus-pituitary system have opposite effects on red and green vision.

Structure – activity relationship

It appears that plant adaptogens that exhibit a stimulating single dose effect, namely, *R. rosea, S. chinensis* and *E. senticosus,* all contain relatively high amounts of phenolic compounds, particularly phenylpropane or phenylethane derivatives. These compounds are structurally related to the catecholamines, and presumably play important roles in the SAS and CNS systems. In contrast, plants such *P. ginseng, Bryonia alba, E. senticosus* etc, which contain relatively large amounts of tetracyclic triterpenes that are structurally similar to corticosteroids, reveal their stress protective effects and adaptation to stressors after repeated administration for periods 1 – 4 weeks. In these cases, the active components play key roles in the HPA axis-mediated regulation of the immune and neuroendocrine systems.

It is worth noting that, along with the common feature associated with all plant adaptogens, namely, induction of a state of non-specific resistance in stress, these drugs exhibit various specific effects under different conditions. For example, it seems that the most important effects of *R. rosea* extract relate to improvements in mental performance, memory and learning. On the other hand, the extract of *S. chinensis* shows an hepatoprotective effect, produces an improvement in eye vision in darkness, increases stamina, physical performance and working capacity, particularly in tiredness, and is recommended for treatment of patients presenting asternic- and astheno-depressive states. *E. senticosus* exhibits a pronounced adaptogenic effect, increasing the non-specific resistance of the organism to viral and bacterial infections and to other harmful stressors (radiation, cold, noise, negative emotions, and physical load). Furthermore, a dry extract of this adaptogen, taken at a rate of 300 mg/day for 8 weeks, increases the quality of life of elderly patients (Cicero et al., 2004). Chisan®, a fixed combination of all three of these plant adaptogens, has also been shown to increase the quality of life of patients with pneumonia when taken daily during the illness (Narimanyan et al., 2005). In a similar manner, *P. ginseng* significantly increased the quality of life in 338 patients each taking one capsule per day for 12 weeks compared with a control group of 163 patients (Caso Marasco et al., 1996).

Conclusions

Only three of the known plant adaptogens, namely *R. rosea*, *S. chinensis* and *E. senticosus,* exhibit a harmless, "adaptogen-type" stimulating effect on humans leading to improvements in mental performance and learning efficacy after single dose administration: the most active stimulant is that derived from *R. rosea.* The stimulating effects of these drugs are apparent within 30 min after administration and last for at least 4 – 6 h.. The active principles associated with the single dose stimulating effect of the three plant adaptogens are phenylpropane and phenylethane phenolic glycosides, in particular, salidroside (**1**), rosavin (**2**), syringin (**3**) and triandrin (**4**), the latter showing the strongest activity.

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Legends to Figures

Fig. 1. The effect of an extract of *Rhodiola rosea* on learning in rats using an active avoidance method with positive (food) reinforcement (Figure drawn from the data of Petkov et al., 1986).

Fig. 2. The effect of an extract of *Rhodiola rosea* on learning in rats in experiments involving active avoidance tasks with negative (punitive) reinforcement. Maze training started 30 min after oral administration of *R. rosea* extract. Values shown are means ± SEM. (Figure drawn from the data of Petkov et al., 1986).

Fig. 3. The effect of an extract of *Rhodiola rosea* on memory in rats in experiments involving active avoidance tasks with negative (punitive) reinforcement. The memory test applied 24 h after training and on 9 subsequent days following the first retention test: maze training started 30 min after oral administration of preparation. Values shown are means ± SEM. (Figure drawn from the data of Petkov et al., 1986).

Fig. 4. The effect of a single dose of *Rhodiola rosea* extract (administered 30 min before thiopental) on thiopental (50 mg/kg, i.abd.) induced sleep in mice. The duration of sleep was measured by the time that each animal remained laying on its side. (Figure drawn from the data of Petkov et al., 1986).

Fig. 5. **(a)** The stimulating effect of salidroside on mice kept continuously on poles until complete exhaustion; **(b)** The anti-hypnotic effect of salidroside (s/c injection at a dose of 100 mg/kg) and of Rhodiola administered 1 h before the induction of sleep in mice by Medinal. (Figure drawn from the data of Barnaulov et al., 1986).

Fig. 6. The stimulating effects of compounds isolated from roots of *Rhodiola rosea*. Preparations were administrated 6 times within 3 days to the test animals and their

investigative behaviour compared with that of a control group of rats. Subjects were assessed using a "free field" method involving counting the number of oriented standing up activities and entries into segments of an arena for 3 min. On the 4th day, drug was administered to the rats who were then subjected to an electrical current (12 mA for 10 s), in order to decrease their unconditioned oriented reflex, and "free field" counting was conducted 15 min after the electrotrauma. (Figure drawn from the data of Barnaulov et al., 1986).

Fig. 7. The effect on spontaneous movement activity in rats after single dose administration of triandrin, rosavin and syringin. (Figure drawn from the data of Sokolov et al.,1990).

Fig. 8. The arousing effect of triandrin, rosavin and syringin after single dose administration to chloral-hydrate anaesthetised mice. Values shown are means ± SEM. (Figure drawn from the data of Sokolov et al.,1990).

Fig. 9. The stimulating effect of triandrin, rosavin, syringin and cinnamoyl alcohol after single dose administration to sodium barbital anaesthetized mice. (Figure drawn from the data of Sokolov et al.,1990).

Fig. 10. The effect of a single dose of *Rhodiola rosea* extract (10 drops) and salidroside (2.5 mg) on the mental performances of 46 healthy subjects as measured by a text correction test applied 1 h after administration in comparison with a control test applied 1 h before administration. (Figure drawn from the data of Aksenova et al., 1968).

Fig. 11. The effects of extracts of *Eleutherococcus senticosus* and *Panax ginseng* on the mental performance of radio operators assessed 1 h after drug uptake. (Figure drawn from the data of Medvedev, 1963).

Fig. 12. The dynamics of object-stimulus fixation: measurements of speed and precision were assessed 30 minutes after intake of ADAPT-232 and for the following 4.5 h. (Figure reproduced from Bogatove et al., 1994 with permission).

Fig. 13. The effect of stimulants on **(a)** the working capacity at maximal intensity for 30 s (sprint) determined 30 min after administration, and **(b)** the duration of work at a preset high intensity determined 35 min after administration. (Figure drawn from the data of Tuzov, 1968).

Table 1. Results of human studies involving single dose effects of plant adaptogens on physical and mental performance

Reference to study	Number of subjects in the study (*n*)	Study design[a]	Age range of subjects	Daily dose	Type of preparation tested	Duration of study	Effects recorded	Classification of evidence level according to WHO, FDA and EMEA[b]
Aksenova et al., 1968	46	PC, SB	20-28	2.5 mg	Salidroside	Acute	Improved mental performance; reduced the number of errors in Anfimov's correction test; stimulating effect lasting 4 h or more	IIa
Andrejev and Georgijev, 1958	19	?	?	25 drops	*Schizandra chinensis* fruits 70% tincture, 1:3	Acute	Increased muscular working capacity	III
Astanin et al., 1943	13	C, CO	?	2 mL	*S. chinensis* tincture, phenamine, caffeine, 48% ethanol	Acute	Improved running time in 60% of athletes	IIb
Berdyshev, 1995	357 sailors	PC, CO	?	0.25, 0.5, 1.0, 2.0, 4.0 and 8.0 mL	*Eleutherococcus senticosus* extract *S. chinensis* extract	acute	*E. senticosus* improved mental performance in correction test; increased activity of the adrenal cortex (excretion of 17-ketosteroids in the urine), the activity of the sympathetic adrenomedullar system (in orthostatic test), the intensity of metabolic processes (excretion of vitamin C in the urine), and the intensity of red-ox processes. In stress conditions *E. senticosus* decreased adrenal cortex activity and sympathetic nervous system; increased the tonus of the parasympathetic nervous system; moderately intensified excitation of the CNS and of energy metabolism; improved endurance to hypoxia. *S. chinensis* stimulated the activity of the CNS at night (activated excitation processes and normalised nervous processes ratio); increased tonus of the sympathetic part of the autonomic nervous system (having no effect on the parasympathetic part) after night duty; activated the adrenal cortex activity; increased the activity of the cardiovascular and respiratory systems; intensified oxidation-reduction and metabolic processes; improved working ability parameters; reduced parameters of non-specific resistance the organism .	IIa

Bogatova and Malozemov, 1994	60	PC, CO, DB	?	3 capsules	ADAPT-232, fixed combination of standardised extracts of *Rhodiola rosea* (salidroside 3 mg), *E. senticosus* (syringin 3 mg), *S. chinensis* (schizandrin 4 mg), in capsules	acute	Compared with placebo, ADAPT-232 significantly increased short-term memory, speed and reliability in the understanding of information, and precision and accuracy in the ability to reproduce the information in repeated highly sophisticated computer-based tests (Monotonic 2). ADAPT-232 was most effective against a background of pronounced fatigue induced by monotonous night work. The effect was most pronounced in complicated tests and under extreme conditions.	IIa
Bogatova et al., 1997	5 cosmon-auts	PC, DB, CO	?	3 capsules	ADAPT-232, fixed combination of standardised extracts of *R. rosea* , *E. senticosus*, *S. chinensis*, in capsules	acute	ADAPT-232 significantly decreased the number of mistakes (*cf.* with placebo) in complicated psychometric tests 4 h after administration and increased working capacity 1.5 and 4 h after administration to Russian cosmonauts during their training in prolonged isolation (90 days) under conditions of long-term, monotonous work. No significant effect was observed in non-complicated tests.	IIa
Dalinger, 1966	76 skiers at four levels of training	PC	20-25	4 mL	*E. senticosus* tincture	Acute, 40 min or 1.5 h before a competition	Single dose increased working capacity, shortened recovery period in prolonged physical load and at low temperatures.	IIb
De Bock et al., 2004	24	R, PC, DB,CO	19-22	2 capsules	Standardised extract of *R. rosea,* 100 mg in capsule	Acute and for 4 weeks	Acute intake of *R. rosea* improved endurance exercise capacity but showed no effect after daily intake over a 4-week period.	Ib
Eglit et al., 1965	28 athletes	C	?	2,5,10, and 15 mL	*S. chinensis* seed 20% tincture	Acute	Improved the function of the respiratory and cardio-vascular systems, increased muscle power of the hand muscles; reduced the time required by athletes to complete the course Best results were obtained with doses of 5 and 10 ml	IIb
Galochkina, 1948	15	Open study	?	1.6 g	*S. chinensis* fruit powder	Acute	Improved eye retina sensitivity to red 25-30 min after administration	III
Grigorenko and Berdyshev, 1988	200 sailors	C	?	2 mL 2 mL 200 mL 200 mL	*S. chinensis* tincture *E. senticosus* tincture Black tea Coffee	Acute and repeated	*S. chinensis* showed a tonic effect for 4 - 7 h in those on night duties. *E. senticosus* was inactive Repeated uptake (for more than 2 weeks) of coffee and *S. chinensis* produced similar negative effects (insomnia, excitability, etc.).	IIb
Kaliko and Tarasova, 1966	80 healthy students	PC, SB	?	10 drops or	*R. rosea* extract and *Rhaponticum*	Acute	Single and repeated administration of adaptogens improved functional state of the CNS in patients with	IIa

	(control group) and 70 patients with neurosis		 20-50	3 x 10 drops a day 40 drops or 3 x 10 drops a day	*cartamoides* extract	and 10 days	neurosis as characterised by normalisation of the speed and power of neural processes in Ivanov-Smolenski's verbal test with speech-supported locomotor-conditioned reflex measurement. The memory improved and attention became more stable.	
Karo, 1945; Lazarev, 1946	8 males	PC	20-22	3 g 30 mL 30 mL 30 mL 30 mL	*S. chinensis* berry dry, *S. chinensis* berry tincture *S. chinensis* berry decoction *S. chinensis* seed tincture Water and 70% ethanol (controls)	Acute	Increased physical working capacity and physical force of men 1 - 3 h after administration; tincture of *S. chinensis* seed was most active.	IIb
Kochmareva, 1958	122 students	CO, PC, SB	?	2 g 2 mL	*S. chinensis* seed powder *Panax ginseng* tincture	acute	Improved attention in text correction 2 h after drug administration. Both extracts increased quality and quantity of mental work performed.	IIa
Kokhanova et al., 1950	? students	PC	?	3 capsules	*S. chinensis* seed powder, 0.5 g in capsules	Acute and multiple	Increased physical working capacity starting from 2.5 h after single dose administration and lasting for 3 h. More pronounced effect was established against a background of fatigue. After multiple administration *S. chinensis* showed no stimulating effect.	IIa
Komar et al., 1981	254	PC	19-22	20 drops 20 drops 0.3 g	*Rhodiola rosea* 40% ethanol tincture *E. senticosus* 40% ethanol tincture Extract of *R. rosea* rhizome	Acute	Improved mental performance; reduced the number of errors in Anfimov's correction test; increased the accuracy, working capacity and speed of information perception. Stimulating effect lasted 4 h or more	IIa
Lebedev, 1951a Lebedev, 1967	20	CO	21	3 g, 0.036 – 0.168 g	*S. chinensis* seed, extract and fractions, tablets and capsules	acute	Improved accuracy in error correction test. Most active stimulating effect was revealed by a crystalline substance identified as the lignan schizandrin.	IIb
Lebedev, 1955 Lebedev, 1967	23	PC	21-22	0.02 g 0.01 g 0.005 g 0.02 g 0.5 g	Schizandrin Schizandrin Schizandrin Phenamine Glucose	Acute	Schizandrin improved accuracy in the work of telegraph operators at exhaustion compared with control group and those given phenamine.	Iib
	125	C, open	?			Acute	Schizandrin significantly decreased running time in a competition at 3000 m *cf.* with control group	III
Lebedev, 1967	20	CO, PC	21-24	30 mL 30 mL	*S. chinensis* seed tincture	Acute	*P. ginseng* and *S. chinensis* improved accuracy in the work of telegraph operators at exhaustion compared	IIa

				0.02 g 0.5 g	*P. ginseng*, 3% tincture Phenamine Glucose		with controls and phenamine.	
Marina et al., 1994	82	?	?	1, 5, 10 and 20 mg 5 drops	Tyrosol *R. rosea* extract	?	Improved mental performance, reduced the number of errors in Anfimov's correction test	III
Medvedev, 1963	13	PC, SB, CO	21-23	2 mL 2 mL	*E. senticosus* tincture *P. ginseng* tincture	acute	Decreased errors in data sent by radio operators 1 h after drug uptake. Stimulating effect of *E. senticosus* was stronger and more stable than the effect of Ginseng, which was insignificant	IIa
Murtazin, 1946	Study A 45 soldiers; Study B 58 subjects	C C	? ?	6 capsules 6 capsules	*S. chinensis* seed powder, 1 g in capsules	Acute	Mean running time of verum group was shorter than that of the control group in a 20 km marathon ski under stress conditions. Fatigue, muscular pain, shortness of breath and dryness of the mouth were reduced.	IIb
Roslyakova et al., 2000	60	PC, DB	?	?	Rodelim, , fixed combination of standardised extracts of *Rhodiola rosea ,* *E. senticosus*, *S. chinensis*, in tablets	acute	Rodelim improved mental working capacity in computer and correction tests against a background of fatigue. .	IIa
Shevtsov et al., 2003	161	DB, R, PC	19-21	2, 3 capsules	Standardised *R. rosea* extract, 185 mg in a capsule	Acute	Improved visual perception, short term memory capacity, attention span and ability to switch attention and anti- fatigue effect in the psychometric tests.	Ib
Strokina, 1967	40	PC, DB	23-55	120 mg	*E. senticosus* dry extract	Acute and 3 weeks	Improved mental performance determined by a letter correction test	Ib
Trusov, 1953	120 pilots	PC, SB	?	3g	*S. chinensis* seed powder, capsules	Acute	Improved night vision 50-70 min after administration by some 1.5 – 2-fold for 7-8 h.	IIa
Trusov, 1958a	150 health males	PC, SB	21-26	3g	*S. chinensis* seed powder , capsules	acute	Improved eye retina sensitivity to light under dark conditions for 3.5 h in 90% of subjects 1.5 h after drug administration	IIa
Tuzov, 1968	52	PC, SB, R	18-24	2 mL 15 drops 2 mL 2 mL	*E. senticosus* extract *Rhodiola rosea,* extract *Rhaponticum cartamoides* extract *P. ginseng* extract Pyridrol	Acute	*Rhodiola rosea, E. senticosus* and *Rhaponticum cartamoides* increased working capacity at maximal intensity for 30 s (sprint) and duration of work of preset high-intensity 35 min after administration. The effects were more significant under conditions of fatigue.	Ib
Yefimova et al., 1954	7	PC, CO, SB	20-22	1 g	*S. chinensis* seed powder, 0.5 g in capsules	Acute and repeated	Increased physical working capacity by up to 222% *cf.* with control. After repeated administration *S. chinensis* did not increase working capacity, but after a wash-out	IIa

							period, the stimulating effect returned	
Zotova , 1965	85	PC	20-28	5-10 drops	*Rhodiola rosea* 40% ethanol tincture	Acute	Improved mental performance, reduced the number of errors in Anfimov's correction test: the stimulating effect lasted 4 h or more	IIb

[a] Abbreviations employed: ? - data not listed or unavailable; CO - crossover; DB - double-blind; SB – single blind, NC - not controlled; PC - placebo-controlled; C – controlled, R, randomised.

[b] Ia – Meta-analyses of randomised and controlled studies; Ib - Evidence from at least one randomised study with control ; IIa - Evidence from at least one well-performed study with control group; IIb - Evidence from at least one well-performed quasi-experimental study; III - Evidence from well-performed non-experimental descriptive studies as well as comparative studies, correlation studies and case-studies; and IV - Evidence from expert committee reports or appraisals and/or clinical experiences by prominent authorities.

Table 2. The difference between adaptogens and other stimulants

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

Table 3. The values of the correlation coefficients associated with comparisons of effects of *Eleutherococcus senticosus* extract (4 ml) and initial levels of functional parameters in sailors during watches in middle altitudes

Parameter	**Correlation coefficient**		
	Morning (8:00)	**Evening (20:00)**	**Night (4:00)**
Excretion of 17-ketosteroids in urine	0.57	0.31	0.22
Eosinophils of the blood	-0.22	-0.35	-0.26
Orthostatic test	0.59	0.63	0.31
Clinostatic test	-0.68	-0.52	-0.36
Vitamin C excretion in urine	0.62	0.37	0.17
Rotter test	-0.55	-0.4	-0.21
Hench test	-0.48	-0.25	-0.12
Phagocytosis percentage	-0.41	-0.34	-0.23
Phagocytic index	-0.55	-0.43	-0.28
Vascular resistance	-0.53	-0.36	-0.32
Osmotic resistance of erythrocytes	-0.66	-0.42	-0.2

Table 4. The values of correlation index between the effects of *Eleutherococcus senticosus* and *Schizandra chinensis* extracts and changes in functional parameters during a day watch under unfavourable conditions

Parameters	**Index of pair correlation**	
	Eleutherococcus senticosus	***Schizandra chinensis***
Excretion of 17-ketosteroids in urine	-0.55	0.21
Eosinophils of the blood	0.42	-0.16
Energy metabolism	0.34	0.83
Rotter test	-0.33	-0.59
Respiration coefficient	0.15	0.5
Tonus of the sympathetic adrenomedullar system	-0.27	0.78
Tonus of the parasympathetic nervous system	0.69	-0.21
Vitamin C excretion in urine	-0.22	0.4
Total nitrogen excretion in urine	-0.3	0.38
Breathing retention at exhalation	0.58	-0.35
Phagocytosis percentage	0.41	-0.24
Phagocytic index	0.53	-0.16
Vascular resistance	0.39	-0.4
Osmotic erythrocyte resistance	0.45	-0.27
CNS excitation	0.21	0.69
Excitation/inhibition balance in the CNS	0.48	-0.17
Heart rate	-0.36	0.49
Systolic blood pressure	0.18	0.45
Coefficient of the cardiovascular system endurance	-0.46	-0.29
Body temperature	-0.3	0.37

Table 5. Effects of extracts of *Eleutherococcus senticosus* and *Schizandra chinensis* on functional parameters in sailors during night watches in middle latitudes

Parameters	**After a night watch (4:00)**		
	Control	***Eleutherococcus senticosus***	***Schizandra chinensis***
Time of a simple sensorimotor response (ms)	230±1.0	226±1.4	212±2.3*
Endurance to static effort (s)	24.9±0.5	25.6±0.6	27.8±0.6*
Hench test (s)	26.8±0.5	28.9±0.4	26.5±0.6*
Body temperature (°C)	36.30±0.01	36.30±0.01	36.60±0.02*
Heart rate (bpm)	66.2±0.8	68.4±0.9	72.8±1.1*
Systolic pressure (mm Hg)	100±0.8	104±1.3	108±1.3*
Diastolic pressure (mm Hg)	60.5±0.7	62.0±0.9	70.0±1.1 *
Orthostatic test (bpm)	13.1±0.6	14.1±0.8	18.2±0.9*
Clinostatic test (bpm)	16.5±1.0	16.4±1.1	16.2±0.8
Respiration rate (breath/min)	12.4±0.7	13.2±0.6	15.6±0.7*
Diuresis (ml/h)	32.0±2.0	33.5±2.3	41.5±2.5*
Vitamin C excretion in urine (mg/h)	0.41±0.02	0.43±0.02	0.62±0.02*
Excretion of 17-ketosteroids in urine	0.59±0.01	0.52±0.02	0.75±0.03*
Phagocytosis percentage	60±2.4	71±2.8	53±2.4*
Phagocytic index	13±0.57	19±0.62	12±0.55*
Rotter test (min)	14.1±1.3	13.6±0.9	10.5±0.7*

* $P< 0.05$

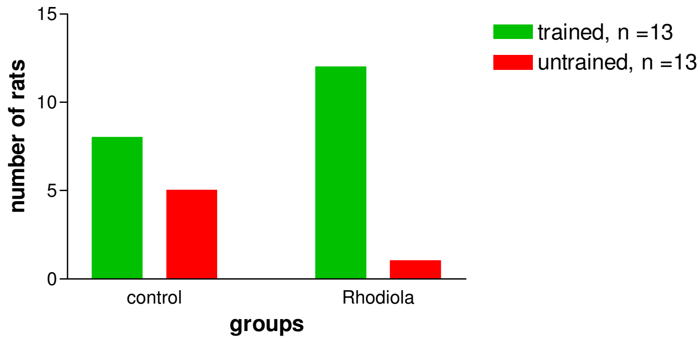


Figure 1

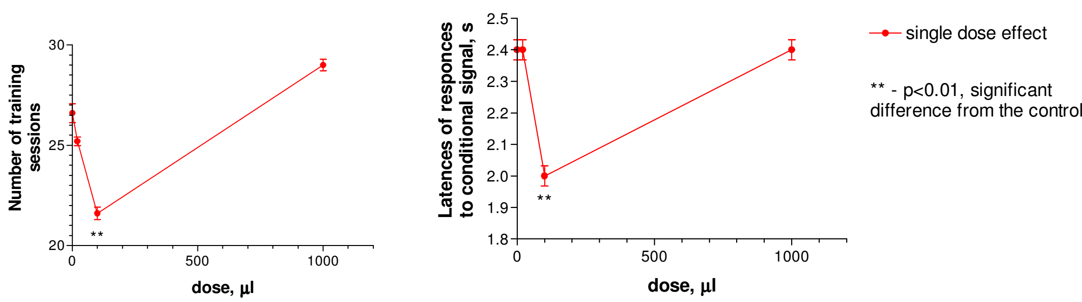
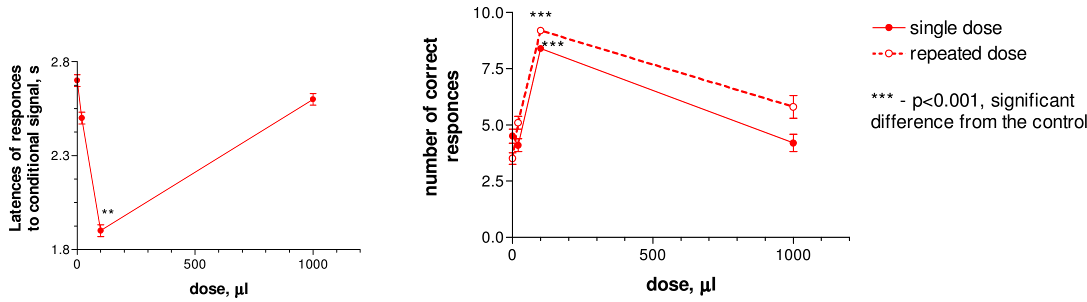


Figure 2



Latences of responces to conditional signal, s
2.8
2.3
1.8
0
500
1000
dose, µl
**
number of correct responces
10.0
7.5
5.0
2.5
0.0
0
500
1000
dose, µl
***
***
single dose
repeated dose
*** - p<0.001, significant difference from the control

Figure 3

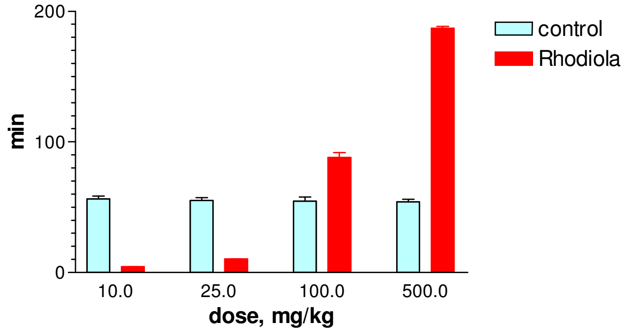


Figure 4

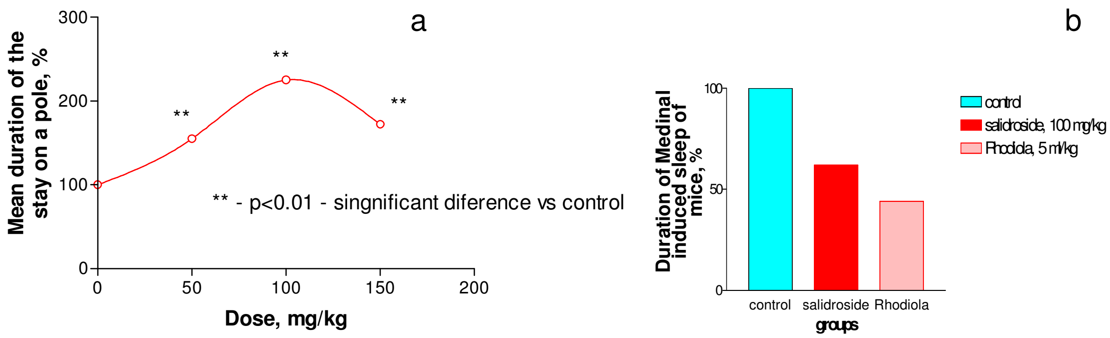
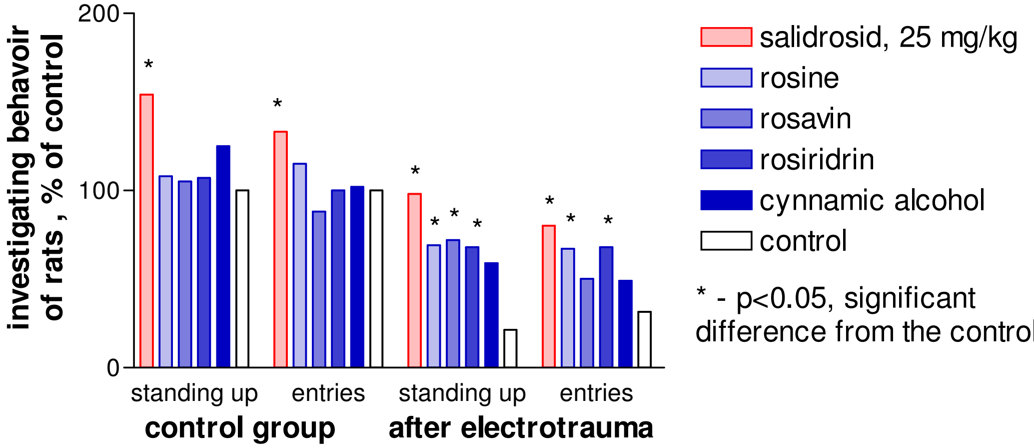
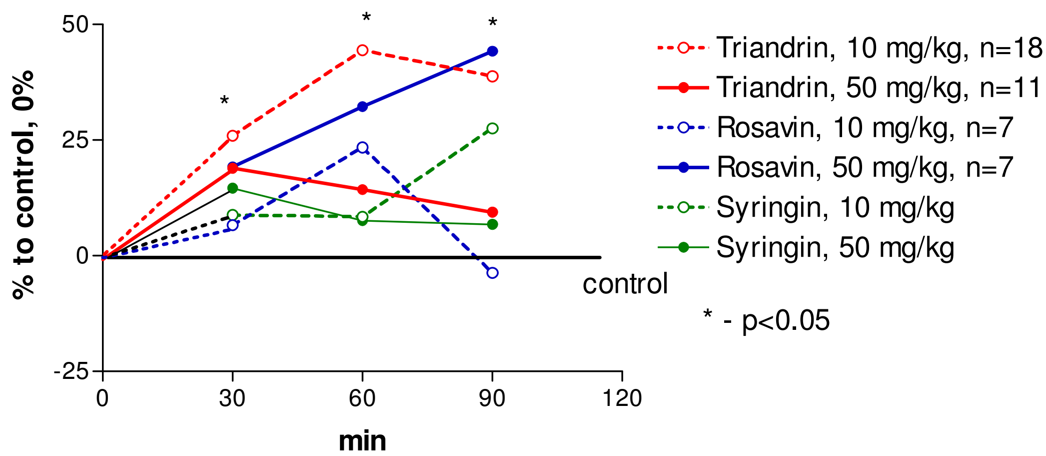

a
Mean duration of the stay on a pole, %
300
200
100
0
**
**
**
** - p<0.01 - singnificant diference vs control
0
50
100
150
200
Dose, mg/kg
b
Duration of Medinal induced sleep of mice, %
100
50
0
control
salidroside, 100 mg/kg
Rhodiola, 5 ml/kg
control
salidroside
Rhodiola
groups

Figure 5



investigating behavoir of rats , % of control
200
100
0
*
standing up
entries
standing up
entries
control group
after electrotrauma
salidrosid, 25 mg/kg
rosine
rosavin
rosiridrin
cynnamic alcohol
control
* - p<0.05, significant difference from the control

Figure 6



50
25
0
-25
% to control, 0%
0
30
60
90
120
min
*
*
*
control
Triandrin, 10 mg/kg, n=18
Triandrin, 50 mg/kg, n=11
Rosavin, 10 mg/kg, n=7
Rosavin, 50 mg/kg, n=7
Syringin, 10 mg/kg
Syringin, 50 mg/kg
* - p<0.05

Figure 7

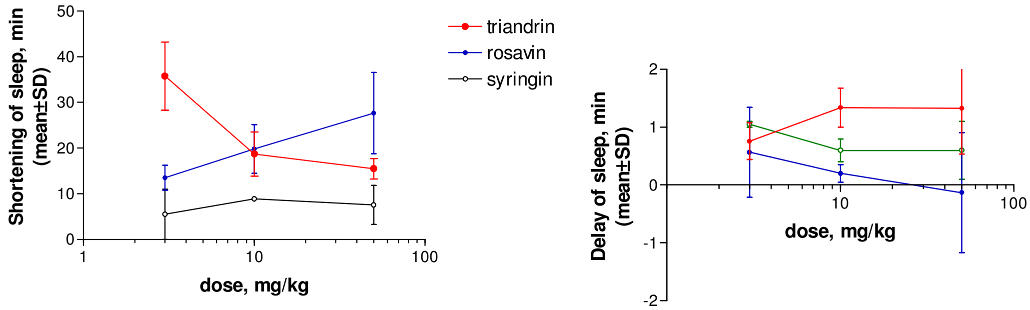

Shortening of sleep, min (mean±SD)
50
40
30
20
10
0
1
10
100
dose, mg/kg
triandrin
rosavin
syringin
Delay of sleep, min (mean±SD)
2
1
0
-1
-2
10
100
dose, mg/kg

Figure 8


Delay of sleep, min
4
3
2
1
0
-1
3
10
dose, mg/kg
triandrin
rosavin
syringin
cinnamoyl alcohol
Shortening of sleep, min
30
20
10
0
3.0
10.0
dose, mg/kg

Figure 9

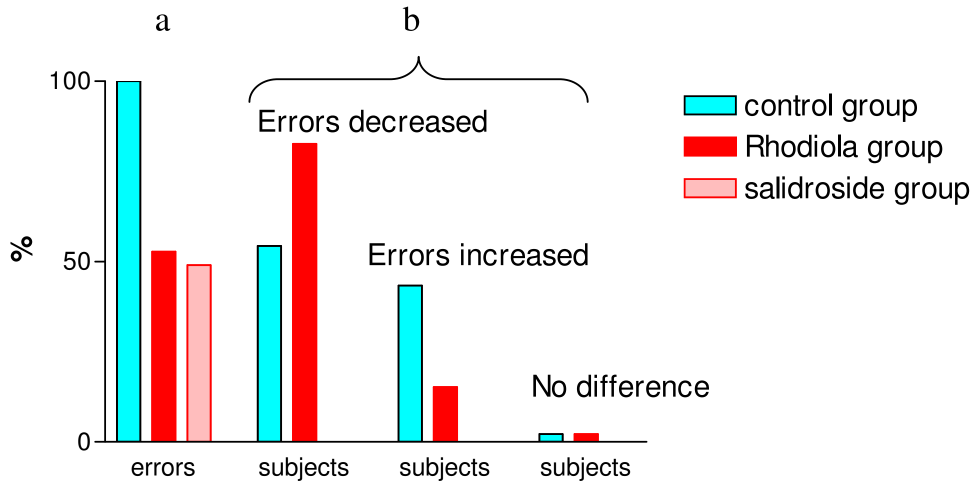

a
b
100
50
0
%
Errors decreased
Errors increased
No difference
errors
subjects
subjects
subjects
control group
Rhodiola group
salidroside group

Figure 10

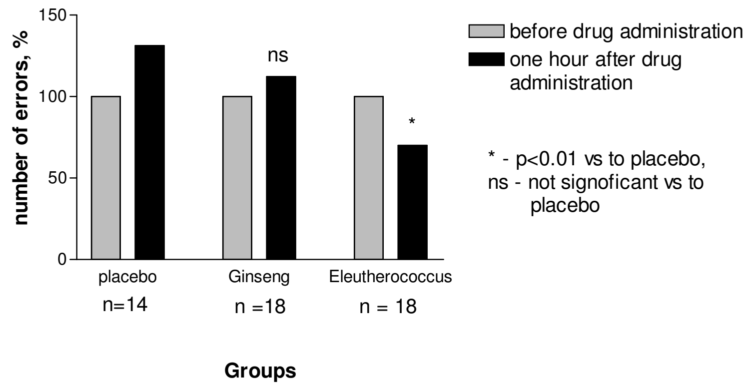
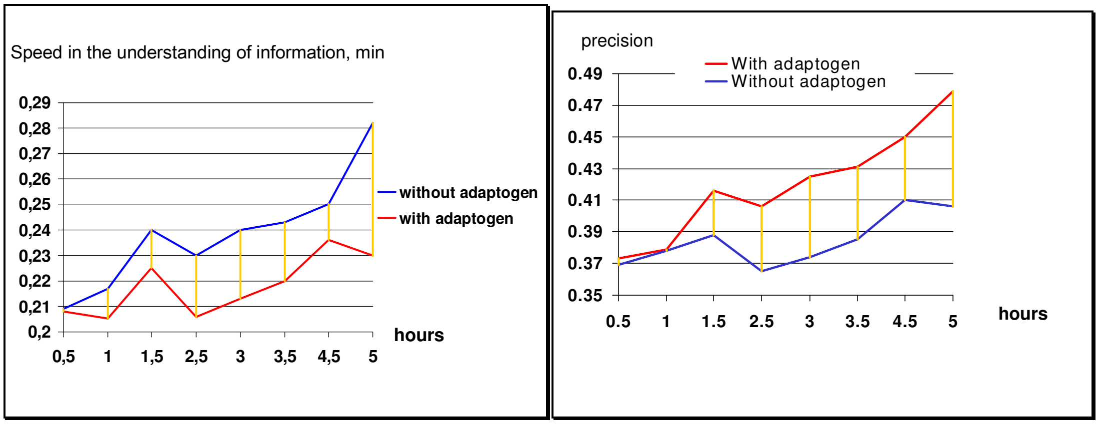

150
100
50
0
number of errors, %
ns
*
placebo
n=14
Ginseng
n =18
Eleutherococcus
n = 18
Groups
before drug administration
one hour after drug administration
* - p<0.01 vs to placebo,
ns - not signoficant vs to placebo

Figure 11



Speed in the understanding of information, min
0,29
0,28
0,27
0,26
0,25
0,24
0,23
0,22
0,21
0,2
0,5
1
1,5
2,5
3
3,5
4,5
5
hours
without adaptogen
with adaptogen
precision
0.49
0.47
0.45
0.43
0.41
0.39
0.37
0.35
0.5
1
1.5
2.5
3
3.5
4.5
5
hours
With adaptogen
Without adaptogen

Figure 12

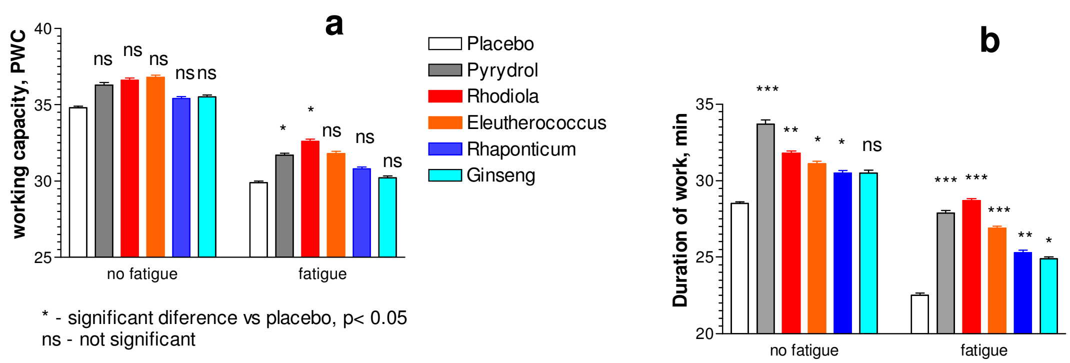
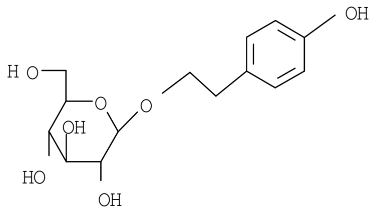
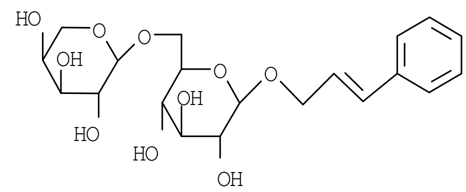

a
b
working capacity, PWC
Duration of work, min
no fatigue
fatigue
Placebo
Pyrydrol
Rhodiola
Eleutherococcus
Rhaponticum
Ginseng
* - significant diference vs placebo, p< 0.05
ns - not significant

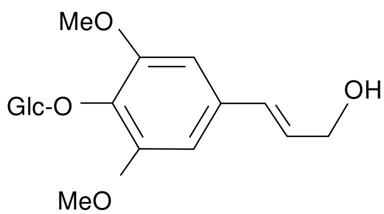
Figure 13



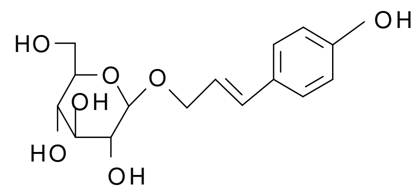
1 Salidroside



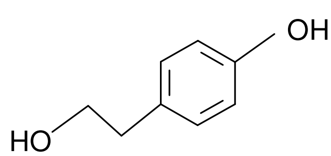
2 Rosavin



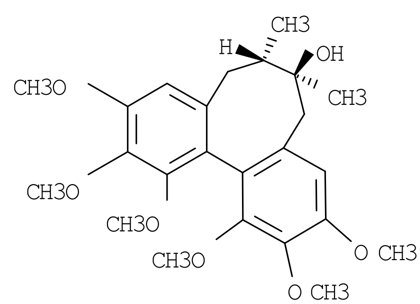
3 Syringin



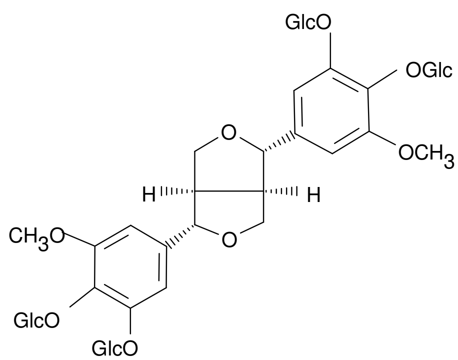
4 Triandrin



5 Tyrosol



6 Schizandrin



7 Eleutheroside B