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A randomized trial of two different doses of a SHR-5 *Rhodiola rosea* extract versus placebo and control of capacity for mental work

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Summary

A randomized, double-blind, placebo-controlled, parallel-group clinical study with an extra non-treatment group was performed to measure the effect of a single dose of standardized SHR-5 *Rhodiola rosea* extract on 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 as a psychostimulant/adaptogen, the other dose being 50% higher. Some 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 161 cadets aged from 19 to 21 years. All groups were found to have very similar initial data, with no significant difference with regard to any parameter. The study showed a pronounced antifatigue effect reflected in an antifatigue index defined as a ratio called AFI. The verum groups had AFI mean values of 1.0385 and 1.0195, 2 and 3 capsules respectively, whilst the figure for the placebo group was 0.9046. This was statistically highly significant ($p < 0.001$) for both doses (verum groups), whilst no significant difference between the two dosage groups was observed. There was a possible trend in favour of the lower dose in the psychometric tests. No such trend was found in the physiological tests.

Key words: *Rhodiola rosea*, SHR-5, single dose, antifatigue effect, clinical trial, efficacy, capacity for mental work

Introduction / Background

A standardized SHR-5 extract from *Rhodiola rosea* radix was shown to have a pronounced antistress effect in previous clinical and pharmacological studies (Darbinyan et al., 2000; Spasov et al., 2000; Boon-Niermeijer et al., 2000). The medicinal plant *Rhodiola rosea* was used medically in France and Sweden during the 18th and 19th centuries, and was mentioned in the 9th edition of the French Pharmacopoeia (Pharmacopée Française, 1974; Virey, 1811; Fournier, 1999; Swedish Pharmacopoeia, 1775; Materia Medica, 1749) and in folk medicine in Germany (Steinegger-Hänsel, 1992; von Striegl, 1928), as well as in Iceland (Halldórsson, 1783; Hjaltalin, 1830). The main use was as a "brain tonic", as a roborant, and to alleviate

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headache. In 1969, preparations based on *Rhodiola rosea* were included in the Pharmacopoeia of the former USSR, and they are well established medically in the USSR and Russia as safe and effective antifatigue drugs and as adaptogens. Since 1985, Rhodiola preparations have also been registered for use as a natural remedy in Sweden as a psychostimulant and adaptogen (Strandberg, 1997; Aly, 1997), and a special extract, SHR-5, was approved in 2001 in Denmark as a herbal medicinal product, being classified as an adaptogen with an indication as an antifatigue drug and for convalescence. The Rhodiola-extract was characterized by HPLC-fingerprint analysis and standardized on the p-tyrosol-glucoside Salidroside (185 mg of the tablet contain 4.5 mg Salidroside). The pharmacological activities of Salidroside (= Rhodioloside) and other phenylpropanoids have been described by Ssaratikov et al. (1968) and Zapesochnaya et al. (1995). The term *adaptogen* was coined and defined in the former USSR as early as 1947 by the Russian scientist Lazarev and was recognised as a functional entity in Russia in 1993. It has recently appeared in US regulatory affairs, being proposed as an example of a "functional and structural" claim by the FDA in 1998 (Notice of proposed rule marketing, Federal Register, April 29, 1998, Anon).

Adaptogens could briefly be defined as metabolic regulators, to date of natural origin, which increase the ability of the body to adapt to environmental (internal and external) factors and to avoid damage from such factors (Brekhman et al., 1969; Panossian et al., First International Conference on Adaptogens, Gothenburg, Sweden 1996, see ref. Panossian et al., 1999).

With regard to the conducting of clinical studies, the question of the optimum dose has been raised. These studies were carried out using a low-dose regimen and repeated-dose treatment, at approximately half the low recommended dose. The official recommendation was for a dosage range mostly based on previous single-dose clinical studies, but with incomplete data on comparisons of different doses in the same double-blind, randomized studies.

It was accordingly decided to carry out a single-dose study using two different doses, one dose representing the standard mean dose, the other dose being 1.5 times this dose. In order to optimize the conditions for this type of study, it is desirable to have as homogeneous a population as possible when selecting subjects.

The study was therefore carried out in a group of young cadets who were all in their training and education period, aged between 19 to 21 years, living in very similar conditions, and all in good mental and physical health. In addition to a placebo group, a fourth, non-treatment group was included as a control, potentially allowing for additional information.

Study design

The study was conducted in accordance with the revised Declaration of Helsinki. The study protocols were reviewed and approved by the Ministry of Health, Moscow. The study was designed as a randomized, double-blind, four-parallel-group study using two verum groups, one placebo group and one control (non-treatment) group to investigate the efficacy and tolerability of the *Rhodiola rosea* SHR-5 extract with regard to nonspecific fatigue and stress. The main objective was to study the antistress and stimulant effects of a single dose of SHR-5 in healthy young males against a background of fatigue and stress. The study drug and placebo were taken as two or three tablets, depending on the group, at 4.00 am, one hour before the second series of tests.

Patient population

Patient inclusion and exclusion criteria

Inclusion criteria: male cadets of a Military Institute of the Russian Federation (RF) Ministry of Defence. The age of the subjects ranged from 19 to 21 years.

Exclusion criteria: heavy smokers (more than 20 cigarettes a day) were excluded from the study.

The study was carried out during the period May 18–23, 2000, in Moscow, when cadets were on night duty performing routine military-service tasks.

Selection of subjects

The subjects were recruited in accordance with inclusion and exclusion criteria after receiving written and verbal information about the study. The study was carried out at the Centre of Sanitary-Epidemiological Inspection of the RF Ministry of Defence.

Sample size

Based on the results of several previous studies with *Rhodiola rosea* (Aksenova et al., 1968; Aksyonova et al., 1966; Darbinyan et al., 2000; Komar et al., 1981; Krasik et al., 1970; Mashkovskij, 1977; Mikhailova, 1983; Saratikov, 1974; Spasov et al., 2000; Tuzov, 1968) as well as two previous studies with SHR-5 extract, a sample size of 4×20 subjects was considered sufficient to obtain significant results. To ensure a sufficient sample size the groups were chosen as follows:

- Group 1: 41 subjects – 2 capsules of verum
- Group 2: 20 subjects – 3 capsules of verum
- Group 3: 40 subjects – 2 capsules of placebo
- Group 4: 20 subjects – untreated control group

Materials and Methods

Study drug

The study preparation: the study was carried out with the preparations in the form of gelatine capsules manufactured by the Swedish Herbal Institute in accordance with GMP standards.

Verum capsules

Raw materials	Content per capsule	Specification
Active substance		
Rhodiola dry extract SHR-5	185.0 mg	SÖI – SP.Ex-006
Excipients		
Microcrystalline cellulose	88.0 mg	Ph. Eur, 2nd Ed.
Magnesium stearate, BSE-free	1.5 mg	Ph. Eur, 2nd Ed.
Silicon dioxide	0.5 mg	Ph. Eur, 2nd Ed.
• Capsule, net weight	275.0 mg	
• Capsule, gross weight	351.0 mg	
Hard gelatine capsule, size No. 1 yellow*, Capsugel	76.0 mg	Ph. Eur, 2nd Ed.

* containing colorants E104, E127 and E171.

Placebo capsules

Raw materials	Content per capsule	Specification
Microcrystalline cellulose	246.0 mg	Ph. Eur, 2nd Ed.
Carrot powder	95.5 mg	Internal
Colour, cocoa	8.1 mg	Internal
Quinoline yellow	0.3 mg	Internal
Riboflavin	0.1 mg	Internal

Rhodiola and placebo capsules had identical organoleptic characteristics and were identical in appearance.

Randomization procedure

The subjects were randomized to one of three treatment groups using simple randomisation. Each bottle, containing 40 tablets, was given a sequential number (1, 2, 3 etc.) with the code concealed from the investigator and subject. The sequential numbers were matched with the order in which the cadets arrived in line. When all bottles had been chosen, the next 20 cadets in the line were chosen as a control (non-treatment) group.

Statistical methods

Two different statistical methods were used:

1. The Mann-Whitney test was used to compare the placebo group and the other three with respect to a well-defined antifatigue index (AFI) for each efficacy parameter. To assess the overall capacity for mental work, a total antifatigue index was calculated, incorporating all individual antifatigue indices except T3e (see below).
2. Student t-test, two-tailed, applied to:

– the intergroup comparison of baseline data

– comparison of "after" with "before" values for each group

Efficacy parameters

Two different categories of efficacy parameters were investigated:

- capacity for mental work, objective parameters
- physiological objective parameters and self-evaluation, subjective parameters (safety parameters).

• *Capacity for mental work:* Three different tests were used: T1, for the assessment of visual perception and information processing of the "correction test" category; T2, for the evaluation of short-term memory; T3, involving higher mental functions, the perception of order. These are briefly described below:

T1 (test 1): This test included the search for pre-assigned symbols embedded among many others that were relevant distracters. A standard test form was a square sheet of paper, 27×2 cm, with a frame containing 1024 rings, 32×32. Of these, 128 rings had a break in a certain position in one of eight positions and were ordered at random (Fig. 1).

Instructions: You are given an array of 32×32 of rings with a break in eight different positions. According to the instruction that is given: cross out rings with the break in the indicated position and place a dot on the others, line by line. Every minute a new instruction will be given, indicating a new position of the break. The position given previously is to be separated by a vertical line. Total time 10 minutes.

Efficacy parameters: Total number of scanned symbols (T1s) and total number of undeleted (missed) or erroneously deleted rings (symbols) (T1e).

T1s is used to measure the speed of task performance (number).

T1e is used to quantify the quality of task performance (number).

T2 (test 2) "Write down digit series" (evaluation of short-term memory capacity)

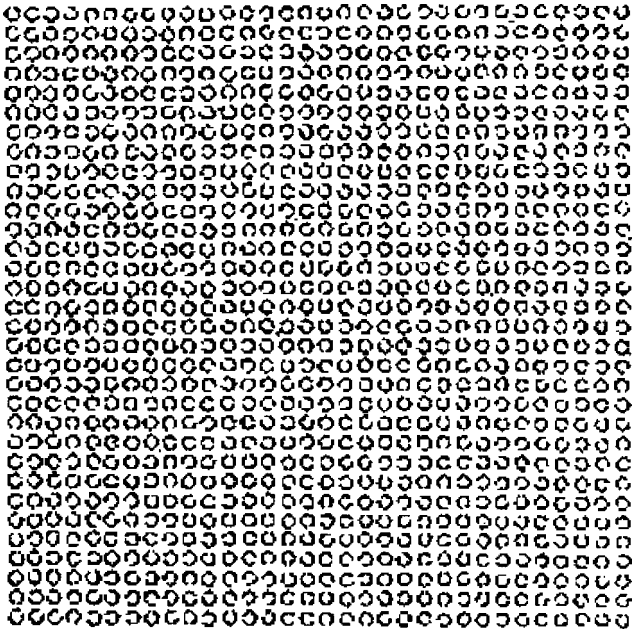


Fig. 1. A form with rings.

This test was used to evaluate the effect of fatigue on the ability to memorize information for a short time. Series of digits (from three to twelve one-digit numbers in each line) forming random lines were used in this test.

The subject was instructed to write down the digits in the same order immediately after a digit series was read out to him once. A short line of digits had to be read out initially before progressing to longer and longer lines, monotonously, with a half-second pause after each digit (Fig. 2).

Instructions: Immediately after hearing a digit sequence, write down the numbers in the same order.

Efficacy parameter: The number of digits in the longest correctly memorized line.

T3 (test 3): "Number arranging".

The test was used to evaluate attention span and ability to switch attention.

A form with two grids was used in this test: the left-hand grid contained 5 (5 cells filled with random two-digit numbers and the right-hand grid contained empty cells. The task involved arranging the numbers, in increasing order, on the left-hand grid into the 25 empty cells of the right-hand grid within 2 minutes (Fig. 3).

The recorded parameters were:

- T3a: the total number of numbers arranged;
- T3e: the number of errors

An evaluation of these two parameters provided an assessment of the results. The total number of arranged numbers (T3a) measured the speed of performance. The number of errors (T3e) reflected the quality of the performance.

- *Physiological parameters:* As parameters indicative of physiological stress and fatigue, two cardiovascular parameters were recorded and analysed: pulse pressures (the difference between systolic and diastolic blood pressure) and pulse rate.

- *Safety parameters:*

– Questionnaires

Self-assessment of general wellbeing

– Medical examination

A physician and a physician's assistant assessed the general state of health of the subjects during the trial.

General health and wellbeing were assessed by means of subjective appraisal on the part of the subjects and were evaluated in questionnaires. The questionnaires were completed at the start of the study and 2 hours after medication.

The investigator noted any adverse effect or event.

The trial regimen

24-hour activity including night duty, and the additional test performance was used as the experimental regimen (Fig. 4).

375	614
1406	2730
39418	85943
067285	306294
3516927	4258396
58397204	29081357
761580329	024865179
2164089573	4790306215
75382170369	39428107536
870932614280	541962836702

Fig. 2. Example.

74	47	95	32	89
68	49	51	25	71
19	62	80	86	42
34	60	79	58	30
5	84	93	26	10

Fig. 3. A sample form for the "number arranging" test.

Outcome measures

In order to have a measure that directly reflected the change in performance before and after treatment, a derived (i.e. calculated) efficacy parameter was used. This was the AFI and was defined as a ratio whereby FI > 1 meant reduced fatigue/increased performance, whilst FI < 1 meant increased fatigue/decreased performance.

When applied to the each efficacy parameter, the AFI was defined as follows:

TIs – Total number of scanned rings:
AFI – TIs after treatment (divided by) TIs before treatment

TIe – Total number of errors: 1
AFI – TIe before treatment (divided by) TIe after treatment

T2 – Correctly recalled digit sequence
AFI – T2 after treatment (divided by) T2 before treatment

T3a – Total arranged numbers
AFI – T3a after treatment (divided by) T3a before treatment

T3e – Number or errors

AEI defined as (T3e before treatment + 1) divided by (T3e after treatment + 1)

Total Antifatigue Index

For the evaluation of the total state of fatigue or level of capacity for mental work, the total AFI was calculated as the mean value of the AFIs in tests 1 to 3, except T3e. This meant that all tests were given equal weighting.

7.00	getting up	
7.15–8.30	physical exercises, cleaning of the barracks	
9.00–14.00	classes, training	
14.00–15.00	lunch	
15.00–16.45	rest, preparation for night duty	
16.45–17.00	questionnaires (not related to the mea surement parameters)	
17.00	beginning of the trial	
17.00–17.15	1	series 1
17.15–17.30	2	series 1
17.30–17.45	3	series 1
17.45–18.00	PE (physiological examination)	
18.00	night duty	
3.00–3.15	light meal	
4.00	medication	
5.00–5.15	1	series 2
5.15–5.30	2	series 2
5.30–5.45	3	series 2
5.45–6.00	PE	
6.00–6.15	questionnaires	
6.15	continuation of the night duty	

Fig. 4. The study regimen.

Results

All subjects were males, 19 to 21 years old, in good mental and physical shape, well above the average, and trained to be able to cope with physical and mental strain and stress. The initial baseline values obtained before treatment showed that all subjects completed the test, and that the variations between the groups of treatment allocation were statistically insignificant (Table 1). Similarly, the initial data on physiological parameters did not reveal any significant differences (Table 2).

Safety parameters

One subject in the placebo group complained of hypersalivation lasting 40 minutes after intake. No other adverse effect or event was recorded. The medical examination undertaken by the physician did not show any trend or sign of impairment in the state of health in any of the subjects, and in a questionnaire completed two hours after medication the subjects were asked to report whether they felt worse than before the trial, perceived no change, or even felt better than before the trial. These answers were tabulated (Table 3) and clearly show that the subjects in the verum groups did not feel worse to any greater extent than those in the other two groups. In fact, subjects tended to feel better after treatment.

Efficacy: Capacity for mental work

Each efficacy parameter (test T1, T2 and T3) was compared before and after medication, and the results are presented in the following three ways:

– Three groups of capacity for mental work with regard to the Total Antifatigue Index (TAFI), comparing the placebo group with the three other groups;

– Each individual test, comparing the Antifatigue Index (AFI) of the placebo group with the three others, using the Mann-Whitney test (rank sum test);

– Each individual test, comparing before- and after-treatment values, using a paired t test.

Table. 1. Baseline data, mean values of scores for each test.

	T1s	T1e	T2	T3a	T3e
Control	806	12.5	6.15	19.7	3.05
Placebo	829	13.7	6.13	18.6	2.83
Rhodiola 2 capsules	812	14.3	5.85	18.5	2.78
Rhodiola 2 capsules	799	11.4	5.95	20.4	2.85

Table 2. Cardiovascular parameters

Unpaired t-test Groups compared	I Placebo		II RR - 2 caps		III RR - 3 caps		IV Control	
Test	B	A	B	A	B	A	B	A
Number of values	40	40	41	41	20	20	20	20
Systolic blood pressure: comparison and mean values								
P value	0.1936		0.7373		0.3219			
P value summary	n.s.		n.s.		n.s.			
Mean	114.9	119.1	113.7	121.1	112.8	119.8	112.0	115.0
Standard deviation	7.467	7.151	7.986	6.472	8.347	5.250	8.944	7.609
Standard error	1.181	1.131	1.247	1.011	1.866	1.174	2.000	1.701
Diastolic blood pressure: comparison and mean values								
P value	0.9400		0.2922		0.9438			
P value summary	n.s.		n.s.		n.s.			
Mean	67.13	71.75	68.41	72.44	67.00	69.25	67.00	68.75
Standard deviation	5.417	5.377	5.527	4.489	8.176	7.482	7.145	6.257
Standard error	0.8565	0.8502	0.8632	0.7011	1.828	1.673	1.598	1.399
Pulse: comparison and mean values								
Mean	67.90	67.90	68.15	66.10	68.50	66.00	68.90	69.30
Standard deviation	5.143	4.223	5.280	4.218	5.385	4.304	5.088	5.555
Standard error	0.8132	0.6678	0.8246	0.6587	1.204	0.9625	1.138	1.242

Table 3. Changes in general wellbeing of the subjects, 2 hrs after medication.

Groups	No. of subjects	Feeling better		No change		Feeling worse	
		n	%	n	%	n	%
Control	20	1	5	14	70	5	25
Placebo	40	7	17.5	28	70	5	12.5
Rhodiola 2 capsules	41	22	53.7	16	39	3	7.3
Rhodiola 3 capsules	20	9	45	8	40	3	15

The Total Antifatigue Index (TAFI) was calculated as the mean value of the individual Antifatigue Indices (AFI) in tests T1s, T1e, T2 and T3a.

There was a highly significant difference between the placebo group and the group receiving Rhodiola capsules. There was no significant difference between the control group and placebo, see Table 4 and Fig. 5.

Results of total number of scanned rings (T1s) before and after treatment showed there was a significant difference in AFI between the placebo group and the group receiving 3 *Rhodiola* capsules. There was no difference between the placebo and the control, but there was a trend towards a significant result ($P \approx 0.08$) in comparison with the group receiving 2 Rhodiola capsules (Table 5 and Fig. 6).

The results of total numbers of errors (correction test – T1e) showed there was a significant difference between the placebo group and the group receiving *Rhodiola* capsules; the difference in AFI between the placebo and the group receiving *Rhodiola* capsules was highly significant (Table 5). There was no significant difference between the control group and the placebo (see Table 5).The results of test T1e comparing the before and after scores using a paired t test showed there was a significant impairment in the results after medication for the control group and the placebo group, whereas there was no significant difference between the results in the two groups receiving *Rhodiola* capsules (Table 6, Fig. 7).

Results of correctly recalled digit sequences (short-term memory test – T2) showed there was a significant difference between the placebo group and the group receiving 3 *Rhodiola* capsules. The difference in AFI between placebo and the group receiving 2 *Rhodiola* capsules was not significant. There was no significant difference between the control group and the placebo (Table 5).There was no significant difference in the number of digits before and after treatment, wither for the placebo or for the two Rhodiola groups. However, there were significant poor results for the control group after treatment (Table 6 and Fig. 8).

Table 4. Difference in the Total Antifatigue Index between placebo and the three other groups, using the Mann-Whitney test. See Fig. 5.

Groups compared			I Placebo		*P*	*P* value summary
Group	Mean	Standard dev.	Mean	Standard dev.		
II Control	0.8852	0.2895	0.9046	0.3205	0.6822	n.s.
III Rhodiola 2 capsules	1.0385	0.2867	0.9046		< 0.0001	***
IV Rhodiola 3 capsules	1.0195	0.2104	0.9046		< 0.0001	***

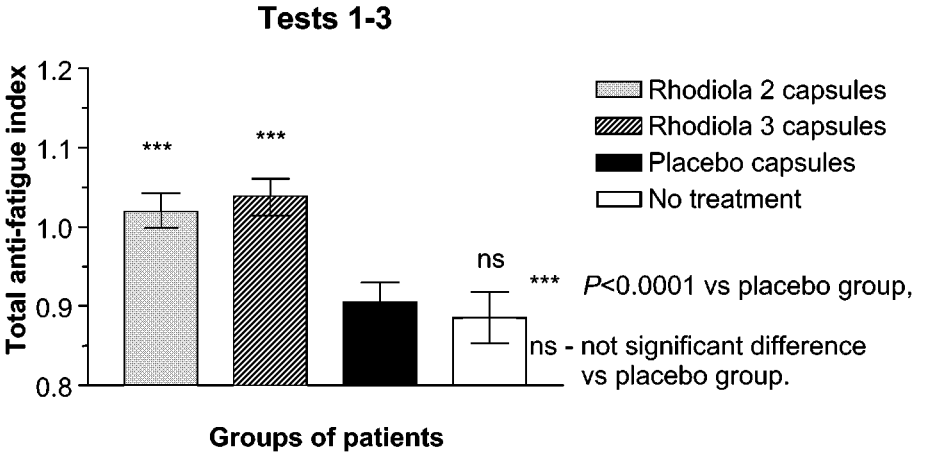


Fig. 5. Total Antifatigue Index: T1s, T1e, T2 and T3a.

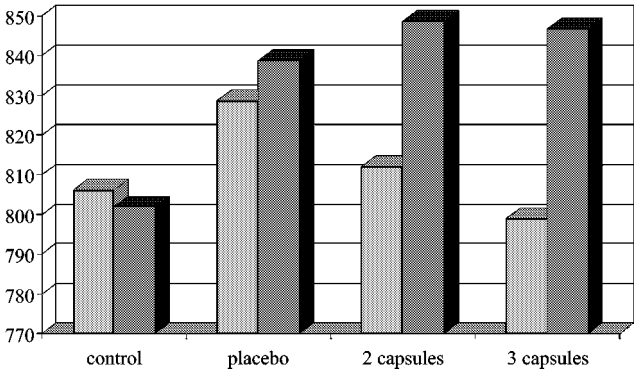


Fig. 6. Changes in the number of rings scanned according to the results of the correction test (T1s). Truncated scale. ■ before, ■ after

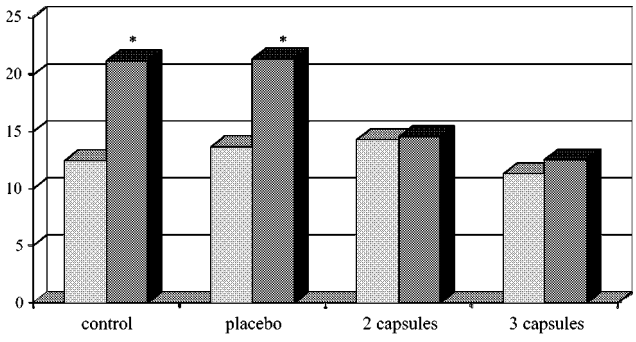


Fig. 7. Changes in the number of erroneously scanned rings according to the results of the correction test (T1e). * the results are statistically significant.; ■ before, ■ after

Results of the total arranged numbers (Test – T3a) showed there was a significant difference between the placebo group and the groups receiving *Rhodiola* capsules, but not between the two dosage schedules (Table 5). Both the placebo and the control showed impaired results, whilst both verum groups improved their scores, see Table 6 and Fig. 9. The difference in AFI between the placebo and the group receiving *Rhodiola* capsules was even more significant. There was no significant difference between the control and the placebo (Table 5 and Fig. 9)

Results of arrangement of numbers (quality of performance test – T3e) showed there was a significant difference between the placebo group and the groups receiving 3 *Rhodiola* capsules, and an almost significant difference between the placebo and the group re-

Table 5. Results test. Antifatigue Index for each test. Statistics according to Mann-Whitney test.

Group	Mean	Placebo	*P*	*P* value summary
Test: T1s-Groups compared				
Control	0.995 ± 0.025	1.020 ± 0.021	0.5451	n.s.
Rhodiola 2 capsules	1.052 ± 0.016	1.020 ± 0.021	0.0839	n.s.
Rhodiola 3 capsules	1.071 ± 0.016	1.020 ± 0.021	0.0223	*
Test: T1e-Groups compared				
Control	0.7440 ± 0.4943	0.6853 ± 0.4358	0.5724	n.s.
Rhodiola 2 capsules	1.009 ± 0.4542		< 0.0001	***
Rhodiola 3 capsules	1.8765 ± 0.2647		0.0113	*
Test: T2-Groups compared				
Control	0.8810 ± 0.1734	1.007 ± 0.2402	0.1785	n.s.
Rhodiola 2 capsules	1.043 ± 0.2128		0.0987	n.s.
Rhodiola 3 capsules	1.107 ± 0.2519		0.0328	*
Test: T3a-Groups compared				
Control	0.9115 ± 0.0870	0.9285 ± 0.0445	0.844	n.s.
Rhodiola 2 capsules	1.050 ± 0.0417		0.003	**
Rhodiola 3 capsules	1.024 ± 0.0256		0.018	*
Test: T3e-Groups compared				
Control	0.9103 ± 0.1363	0.9262 ± 0.1428	0.514	n.s.
Rhodiola 2 capsules	1.1014 ± 0.1882		0.051	(*)
Rhodiola 3 capsules	1.3014 ± 0.2272		0.023	*

Table 6. Results: "Capacity for mental work" parameters. Actual scores, before and after treatment using paired t-test.

Groups	No. of subjects	before medication	after medication	*P*	*P* value summary
Group T1s: No. of corrected symbols. See Fig. 6.					
Control	20	806.2 ± 27.24	801.85 ± 29.84	0.8105	n.s.
Placebo	40	828.68 ± 17.62	838.83 ± 16.33	0.5272	n.s.
Rhodiola 2 capsules	41	812.0 ± 17.28	848.78 ± 14.11	0.0022	**
Rhodiola 3 capsules	20	798.95 ± 23.09	846.8 ± 22.91	0.0007	***
Group T1e: Number of errors. See Fig. 7.					
Control	20	12.45 ± 1.49	21.2 ± 3.09	0.0037	**
Placebo	40	13.68 ± 1.65	21.38 ± 1.84	< 0.0001	***
Rhodiola 2 capsules	41	14.34 ± 1.75	14.56 ± 1.78	0.2544	n.s.
Rhodiola 3 capsules	20	11.35 ± 1.65	12.55 ± 1.42	0.0707	n.s.
Group T2: No. of digits in a line. See Fig. 8.					
Control	20	6.15 ± 0.38	5.3 ± 0.32	0.0091	**
Placebo	40	6.13 ± 0.25	6.08 ± 0.28	0.7999	n.s.
Rhodiola 2 capsules	41	5.85 ± 0.30	5.98 ± 0.27	0.08218	n.s.
Rhodiola 3 capsules	20	5.95 ± 0.22	6.5 ± 0.32	0.0773	n.s.
Group T3a: No. of numbers. See Fig. 9.					
Control	20	19.7 ± 1.29	17.6 ± 1.03	0.1123	n.s.
Placebo	40	18.63 ± 0.69	17.35 ± 0.63	0.0232	*
Rhodiola 2 capsules	41	18.51 ± 0.74	19.2 ± 0.52	0.1706	n.s.
Rhodiola 3 capsules	20	20.4 ± 0.85	20.8 ± 0.82	0.4773	n.s.
Group T3e: No. of errors. See Fig. 10.					
Control	20	3.05 ± 0.52	2.45 ± 0.38	0.3090	n.s.
Placebo	40	2.83 ± 0.32	2.75 ± 0.32	0.8386	n.s.
Rhodiola 2 capsules	41	2.78 ± 0.27	1.73 ± 0.25	0.0005	***
Rhodiola 3 capsules	20	2.85 ± 0.34	1.9 ± 0.31	0.0108	*

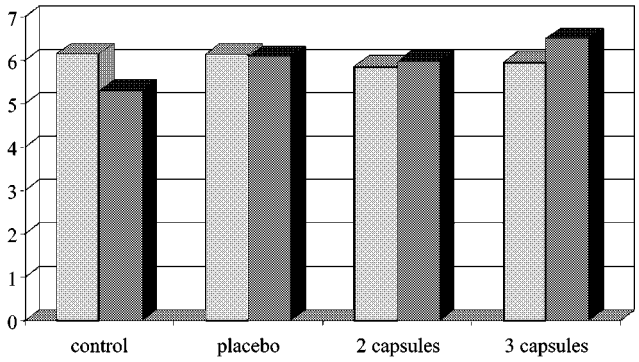


Fig. 8. The results of the short-term memory test (T2).
before, after

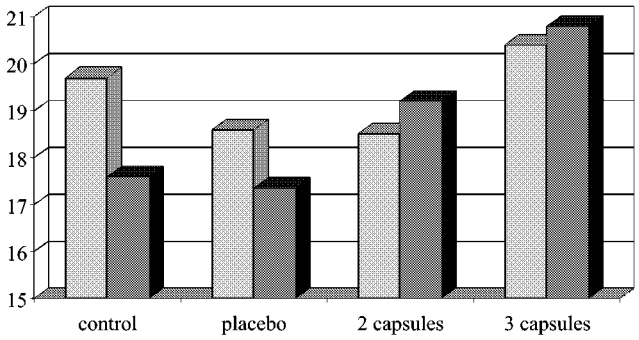


Fig. 9. Changes in the amount of scanned information according to the results of the "number arranging" test (T3a).
before, after

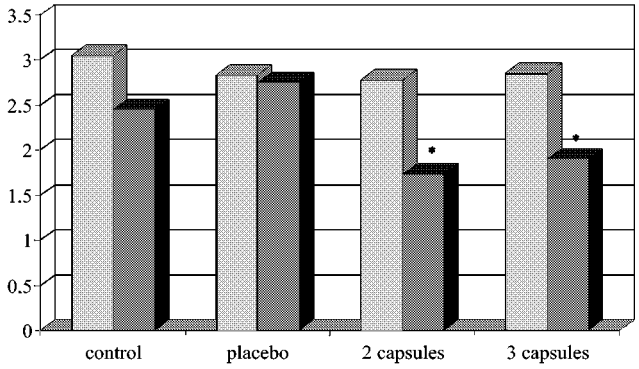


Fig. 10. Changes in the number of errors in the scanned information according to the results of the "number arranging" test (T3e).
* the results are statistically significant; before, after

ceiving 2 capsules ($P = 0.051$) but not between the control group and the placebo (Table 5).There was a significant improvement in the results in the two Rhodiola groups after treatment. The results in the control group and the placebo group were not statistically different

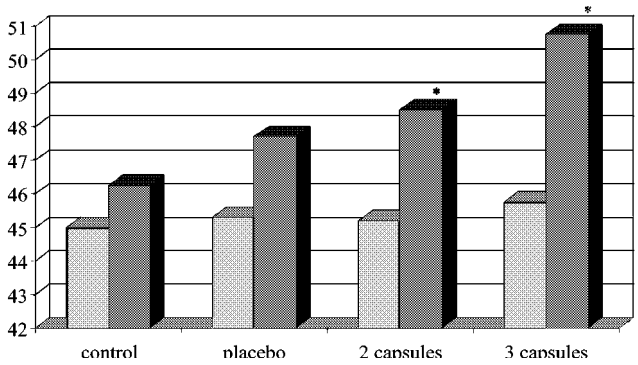


Fig. 11. Changes in the pulse pressure after the intake of the study preparation compared with the placebo-treated and control groups.
* the results are statistically significant before, after

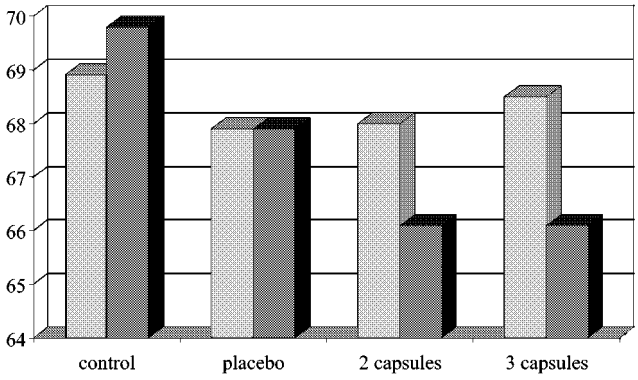


Fig. 12. Changes in the pulse rate after the intake of the preparation compared with the placebo-treated and control subjects.
* the results are statistically significant; before, after

before and after the treatment (Table 6 and Fig. 10). The definition of the AFI does not allow for ratios with a zero in the denominator. Consequently, a modified index was defined and used for the above calculations:

Anti-Error Index (AEI) = (T3e, before + 1) divided by (T3e, after + 1)

The value of the physiological parameter pulse pressure was a parameter derived from the three cardiovascular parameters, systolic and diastolic pressure and pulse rate. This parameter was used to compare outcome between the groups. There was a significant difference between the placebo group and the 2 groups receiving *Rhodiola* capsules, but no significant difference between the control group and the placebo (Table 7 and Fig. 11). Changes also appeared in the pulse rate after the intake of the preparation compared with the placebo-treated and control subjects (Table 7 and Fig. 12).

Discussion

The main objective of the investigation was to show the difference in efficacy between the two doses of the study drug relative to the placebo. An extra non-treatment group was incorporated as an additional reference. The design of the study implies that special attention should be given to possible asymmetry between the groups, reflected in differences in baseline data and other features indicating a lack of homogeneity between the populations of the groups. The discussion is therefore divided into three parts: intrinsic group differences, analyses of differences and similarities between groups that took the two doses, and an overall evaluation and conclusion.

Intrinsic group differences

The base-line values (Table 1 and 2) demonstrate that the overall differences between the placebo group and the other groups were small enough to allow the conclusion that any differences between the groups were minor and negligible. This conclusion is further reinforced by the following observation.

Based on the assumption of an appropriate (non-biased) selection procedure and homogeneity between groups, a certain placebo effect or trend is to be expected, or in other words: a total absence of signs of a placebo effect could even be an argument against the basic assumption of intergroup homogeneity. A cursory inspection of the results, presented in the tables above, directly shows that the mean values of Total AFI, TIs, T2, T3a, T3e, together with the physiological parameters, pulse pressure and pulse rate, are all higher in favour of the placebo group as compared with the control group.

All in all, these two investigations constitute a cogent argument in favour of the assumption of a high degree of similarity between the groups, satisfying the criteria given above.

Comparison between the two dose levels

The total AFI, combining a measurement of amount of work per unit of time and quality of work (number of errors), indicated a highly significant difference between the two verum groups and the placebo group ($P < 0.001$). There was no obvious difference between the two different dosage groups, whilst there was a possible indication of greater efficacy in the low-dose group (Fig. 5).

The overall picture, reflected in the total AFI, shows there was no significant difference in efficacy between the dosages. Looking for similarities between the two groups, the results in tests TI and T3 seem to indicate that the study drug SHR-5 had a more definite effect on the quality of work than on the quantity. This is well in line with the general recognition of *Rhodiola rosea* as a phyto-adaptogen, differing from a conventional CNS drug.

Physiological parameters

Table 7 and figures 11 and 12 show there was virtually no difference between the two dosages, whereas the pulse pressure indicated a statistically significant beneficial physiological effect in the verum groups versus the placebo group.

Table 7. Changes in the pulse pressure after the intake of the study preparation compared with the placebo-treated and control groups.

Groups	No. of subjects	Pulse pressure		*P*
		before medication	after medication	
Control	20	45.0 ± 1.66	46.25 ± 1.69	0.065
Placebo	40	45.3 ± 1.76	47.7 ± 1.01	
Rhodiola, 2 capsules	41	45.2 ± 1.07	48.5 ± 0.99	0.007
Rhodiola, 3 capsules	20	45.75 ± 1.96	50.75 ± 1.32	0.007

Conclusion

Taking the mental and physiological parameters together, the study does not reveal any demonstrated difference in efficacy, or even a minor consistent trend in favour of one of the groups. (Both groups performed highly significantly better compared with the placebo group.) This seems to imply that both doses in the trial are either close to the optimum dose or quite far from it. If one attaches importance to the well-established use in Russian medicine together with a large number of clinical studies of various levels of evidence, the optimum dose will be within a range of approximately 0.5 to 3 times the lowest dose in this study. These facts clearly indicate the first possibility, i.e. the optimum single dose of SHR-5 is close to the doses used in this study.

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