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A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of *Rhodiola rosea* SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen.

A. A. Spasov[1], G. K. Wikman[2], V. B. Mandrikov[1], I. A. Mironova[1], V. V. Neumoin[1]

[1]Volgograd Medical Academy, Volgograd, Russia
[2]Swedish Herbal Institute, Göteborg, Sweden

Summary

The objective was to investigate the stimulating and normalizing effect of the adaptogen *Rhodiola rosea* extract SHR-5 in foreign students during a stressful examination period. The study was performed as a double-blind, randomized and placebo-controlled with low repeated dose regime. The study drug and the placebo were taken for 20 days by the students during an examination period. The physical and mental performance were assessed before and after the period, based on objective as well as on subjective evaluation. The most significant improvement in the SHR-5 group was seen in physical fitness, mental fatigue and neuro-motoric tests ($p < 0.01$). The self-assessment of the general well-being was also significantly ($p < 0.05$) better in the verum group. No significance was seen in the correction of text tests or a neuro-muscular tapping test. The overall conclusion is that the study drug gave significant results compared to the placebo group but that the dose level probably was suboptimal.

Key words: *Rhodiola rosea* SHR-5, mental fatigue, controlled double-blind study

Introduction

The problem of strain and stress on students during examination periods is well- known. Foreign students are in particular exposed to stress due to factors such as adaptation to different climate and insufficient knowledge of the language, social and cultural conditions (Petrov et al., 1997). It has been repeated that 90 % of Indian students suffered from mental discomfort and excessive fatigue during the first years (Mandrikov et al., 1998).

Phytoadaptogens are a class of drugs which increase the capacity to adapt to stressful conditions and which have been used medicinally since the 1960's in the former USSR. The most extensively researched are *Aralia mandschurica, Eleutherococcus senticosus*, *Rhodiola rosea* and *Schizandra chinensis* (Wagner et al., 1994; Brekhman and Dardymov, 1969). Of these, *Rhodiola rosea* has the most pronounced effect on mental fatigue during stress and strain (Saratikov et al., 1987), although all of them have some effect on mental and physical work capacity against a background of fatigue and stress. The aim of this study was to investigate the effect of a repeated low-dose regimen of a special extract of *Rhodiola rosea* radix, SHR- 5, on a group of students from India, during an exam period with respect to both physical fitness and mental well-being and capacity.

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Materials and Methods

Study drug

The test medication (verum and placebo) was manufactured by Teknofarm, Moscow. The extract was manufactured by Swedish Herbal Institute, Sweden, according to GMP. The test medication was in the form of white and sugar-coated tablets, with the following composition: Placebo, Lactose 50 mg, Calcium phosphate, Solanum amylum, Avicel and Magnesium stearate; Verum, Extr. sicc. *Rhodiola rosea* radix SHR-5 50 mg, Calcium phosphate, Solanum amylum, Avicel and Magnesium stearate; Each jar of tablets contained 40 tablets to be taken twice for 20 days; Coating, for verum and placebo, saccharose, calcium carbohydrate, magnesium silicate, polyvinylpyrrolidone, titanium dioxide. Verum and placebo tablets were produced with identical organoleptic appearance and were indistinguishable from one other.

Study Design

The study was performed in compliance with the revised declaration of Helsinki. The protocols of the study were reviewed and approved by the Ministry of Health, Volgorad. The study was designed as a randomised, double-blind, two parallel groups study using a verum group and a placebo group to investigate the efficacy and tolerability of *Rhodiola rosea* extract SHR-5 on non-specific fatigue and stress. The main objective was to study the anti-stress and stimulatory effects of SHR-5 in healthy foreign students during a stressful exam period and with a repeated low-dose regimen. The study drug was to be taken in two tablets a day for 20 consecutive days.

Patient Population

• Patient inclusion criteria:
Male students from India, 17–19 years old, during their first year at Volgograd Medical Academy during an examination period.

• Patient exclusion criteria:
Students suffering from chronic illnesses such as cardiovascular diseases, diabetes, etc.; students addicted to alcohol, medicines or tobacco (more than 20 cigarettes per day). Students with diagnosed nervous problems were also excluded.

• Selection of patients:
The students were recruited according to inclusion and exclusion criteria after having received written and verbal information about the study. The study was carried out at the Volgograd Medical Academy at the Research Institute of Pharmacology during December 1998. The responsible investigator was Dr. I. A. Mironova.

• Sample size:
Based on results from earlier studies with *Rhodiola rosea* and other adaptogens (Aksenova et al., 1966; Komar et al., 1981; Lapaev, 1982; Tuzov, 1968) it was extrapolated, assuming a 30 % difference between the treatment group and placebo that a sample size of 2 x 20 subjects would be sufficient to yield a significance level of 0.05.

• Randomization procedure:
The students were randomized to one of two treatment groups using simple randomization. Each jar, containing 40 tablets, was given a sequential number (1, 2, 3, etc.) with the code concealed from the investigator and student. The sequential numbers were matched with the order of arrival of the students.

• Statistical methods:
All statistical analysis was performed using the Students-test, two sided, with the assumption of normal distribution. All tests were performed on two occasions: the first on the day before test medication was administered and the second after 20 days of administration of medication.

• Efficacy parameters:
Physical fitness was measured using two parameters: physical work capacity as given by the veloergonomic test PWC-170 as measured in the units kg/min. The test is a two step dosed physical loads: first step of 125W and second step at 150W, lasting for 9 minutes. The test is based on work capacity at a heart-rate of 170.
Details of PWC-170: PWC-170

$$= N1 + \frac{(N2\text{-}N1) \times (170\text{-}f1)}{f2 - f1}$$, where

N1 and N2: are the values for two sequential loads in kg/min.
f1 and f2: are heart beats per minute at the end of each load.
where N1 and N2 are the values of two sequential loads in kg/min and f1 and f2 are the respective heart rate values at the end of each step (1W= 6.11kpm/min)

The second parameter was an increase in pulse rate immediately following the ergometric test, as compared with the pulse rate just before

• Psycho-motoric function:
1. Maze test: This was assessed using a spiral maze test where subjects moved a "pen" from the center of a spiral without touching small obstacles. The accuracy of movement was calculated from the number of touches

and the time taken to complete the task in seconds. The test is a variant of Gibson's Spiral test (Gibson, H.B., Spiral Maze, London University Press, 1961).

2. *Tapping test:* The functional status of the neuromuscular system was assessed using a tapping test. The students were asked to press a button as often as possible during 30 seconds. The total number of toppings was recorded.

- **Mental work capacity:**

Correction of text test: speed of performance and concentration ability were assessed by correction of a text where the student was asked to cross-over letters/symbols and given combinations, according to rules; as quickly as possible during 2 x 5 minutes.

- **Example of rule:**

"Cross over all A:s and I:s, but only when not followed by an E". The number of crossed letters/combinations was recorded together with the number of incorrectly crossings (mistakes). The test is a standard Russian psychometric test called Ivanov-Smolensky symbol tables.

- **Tests based on self-evaluation:**

Self-evaluation of fatigue: the students were asked to answer a specially Russian designed psychometric test, according to a special questionnaire. Scores were assigned in points to this test. The students were asked to, according to a special scoring system, evaluate signs of fatigue in terms of experienced deviation from their "normal" state. Examples of signs: various forms of fatigue, sleeping pattern and need for sleep, mental discomfort, instability of mood at different times etc.

- **General well-being test:**

(SAM test) The students were asked to self-evaluate the following according to a 5-point scale: general state, degree of activity, mood, and motivation to work. These parameters were each evaluated and the mean value of these for each student was used as a measure.

- **Safety parameters:**

Any adverse effect was noted by the investigator.

Results

Anthropocentric data

All subjects were male between 17–19 of age, in both groups. Outcome measures: compliance: All students completed the test according to the protocol and no adverse effects were observed. Significant improvements could be seen as measured by the physical fitness tests, psychomotoric test, and mental fatigue test, and in general well-being (see Table 1).

A display of some of the baselines and after treatment values is given in table 2 to give the reader an idea of the actual mean-values etc. for some of the objective parameters.

Table 1. Results given as a ratio of performance after treatment/before treatment. Mean-values and standard deviations.

Physical fitness	Placebo	Verum	Improvement of verum versus placebo
1. **PWC-170**	1.12 ± 0.09	1.20 ± 0.07	$p \sim 0.1$
2. **Increase of pulse-rate PWC- exercise**	0.91 ± 0.09	0.72 ± 0.10	$p < 0.05$
3. **Neuro-motoric fitness:**			
a. Accuracy of movement versus speed in maze test	1.01 ± 0.015	0.49 ± 0.13	$p < 0.01$
b. Tapping test: number of tappings during 30 seconds.	1.10 ± 0.03	1.04 ± 0.04	n.s.
Mental capacity: **Correction test:**			
a. Speed of performance	1.31 ± 0.12	1.36 ± 0.31	n.s.
b. Accuracy of performance (number of mistakes)	0.77 ± 0.14	0.67 ± 0.27	n.s.
General well-being: emotional state, motivation to work scored according to SAM-questionnaire	0.98 ± 0.08	0.90 ± 0.11	$p < 0.05$
Mental fatigue: Self-assessment (scores)	1.21 ± 0.18	0.70 ± 0.09	$p < 0.01$

Discussion

An extensive amount of pharmacological and clinical research has been carried out on preparations based on *Rhodiola rosea* for more than 30 years, demonstrating its effectiveness as an adaptogen. A good summary of material up to 1987 is found in Krasik's and Saratikov's book "*Rhodiola* as a valuable medicinal plant" (Tomsk University Press, 1987).

The present pilot study produced results which were considered consistent with the general use of *Rhodiola rosea* preparations during periods of mental fatigue and stress. The most pronounced results were seen in the improvement in psychomotoric function ($p < 0.01$) and mental fatigue ($p < 0.01$). The general well-being test also produced clearly significant results which should be expected for an adaptogen. The parameters assessing physical fitness were as follows: Physical work capacity and increase in heart beat after exercise gave significant improvement for the SHR-5 group compared to placebo ($p < 0.05$). The neuro-motoric maze-test measuring accuracy versus speed showed a very significant result in the treatment group with a 50 % improvement as compared to placebo.

The effects of *Rhodiola rosea* preparations have been documented in an extensive body of research and medical experience, as enhancing mental performance in stressful situations. (Marina et al., 1994; Saratikov, 1987). Thus, somewhat unexpectedly, the correction test did not show any significant improvement for either the number of correct errors or number of mistakes for the verum group. This is in contrast to earlier studies both with Rhodiola (Marina et al., 1994) and with other adaptogens (see Table 2) (Gubchenko et al., 1986). Comparing before and after treatment values gave a slight difference of the improvement between the verum group and the placebo group appears with respect to both number of corrected symbols and mistakes made. In percentage, the increase in number of corrected symbols are 38 % and 30 % whereas the reduction of mistakes are 32 % and 26 % in the verum group and placebo group respectively.

However in earlier studies the number of errors and the number of mistakes have often been correlated yielding a coefficient of success (A) according to the formula: $A = (C - H) : (M + B)$, where C is the number of over-crossed symbols, H the number of mistakes, M the total number of symbols and B number of not recognised (missed) symbols. With this in mind it cannot be excluded that a similar method would have given a somewhat different result for the verum group as compared with the placebo group. But as the number of unrecognised (missed) symbols were not recorded in the present study, the mentioned coefficient cannot be calculated.

The tapping test did not reveal any difference between the groups with regard to the maximum frequency of tappings per 30 seconds. A significant difference between the groups would have implied a clear neuromuscular state of fatigue, which probably not is to be expected in a psychological stress situation among young persons.

Moreover, it should be emphasized that the present study differs in one important respect from earlier ones as regards to the dose. The majority of single-dose studies are based on over 3 times the dose used in this study. Furthermore the use in official medicine for the corresponding course of treatment (20 days) is given by Medical Drugs (Mashkovskij, l996) as at least twice the dose and up to 6 times the dose of that used in the present study. Furthermore, in psychiatric practice, the dose is approximately 15 times as high during 1–2 months of treatment, mainly in asthenic syndromes. Taking these differences into account, the results could in fact be seen as encouraging in view of the low dose investigated. Future studies of this kind should aim at

Table 2. Descriptive statistics: Baseline and after-treatment values of some objective parameters (with two figures accuracy). Mean-values and standard deviations.

Parameters	Placebo		*Rhodiola rosea* extract, SHR-5	
	before	after	before	after
PWC-170 (kgm/min)	810 ± 43	920 ± 52	810 ± 42	980 ± 40
The accuracy of muscular movements	14 ± 4.7	12 ± 3.2	12 ± 3.5	6 ± 2.4
The number of corrected symbols	230 ± 21	300 ± 13	220 ± 15	310 ± 17
The number of mistakes in the correction table (%)	27 ± 5.5	20 ± 6.1	23 ± 4.5	15 ± 5.4
Tapping test (the number of tappings per 30 seconds)	180 ± 5.5	190 ± 5.0	180 ± 6.0	190 ± 3.0

finding a more optimal dose, presumably somewhat higher, by studying several parallel groups given different doses and following a protocol which takes the results from this study into consideration.

The investigators made a follow-up study of the average exam marks from the examination immediately after the end of the present study. The average mark in the placebo was 3.20 and in the verum group 3.47, which indicates the usefulness of *Rhodiola rosea* during the stressful exam period.

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Address

G. Wikman, Swedish Herbal Institute, Kronhusgatan 11, SE-41105 Göteborg, Sweden.
Tel: +46-31-7116779; Fax: +46-31-7117147;
e-mail: georg.wikman@shi.se.