Phytomedicine, Vol. 7(5), pp. 365–371

http://www.urbanfischer.de/journals/phytomed

Phytomedicine

Rhodiola rosea in stress induced fatigue – A double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty.

V. Darbinyan[1], A. Kteyan[1], A. Panossian[2], E. Gabrielian[2], G.Wikman[3] and H. Wagner[4]

[1]Department of Neurology, Armenian State Medical University, Yerevan, Armenia
[2]Guelbenkian Research Laboratory of Armenian Drug and Medical Technology Agency, Yerevan, Armenia
[3]Swedish Herbal Institute, Gothenburg, Sweden
[4]Institute of Pharmacy, Pharmaceutical Biology, Ludwig Maximilian University, Munich, Germany

Summary

The aim of this study was to investigate the effect of repeated low-dose treatment with a standardized extract SHR/5 of rhizome *Rhodiola rosea* L, (RRE) on fatigue during night duty among a group of 56 young, healthy physicians. The effect was measured as total mental performance calculated as Fatigue Index. The tests chosen reflect an overall level of mental fatigue, involving complex perceptive and cognitive cerebral functions, such as associative thinking, short-term memory, calculation and ability of concentration, and speed of audio-visual perception. These parameters were tested before and after night duty during three periods of two weeks each: a) a test period of one RRE/placebo tablet daily, b) a washout period and c) a third period of one placebo/RRE tablet daily, in a double-blind cross-over trial. The perceptive and cognitive cerebral functions mentioned above were investigated using 5 different tests. A statistically significant improvement in these tests was observed in the treatment group (RRE) during the first two weeks period. No side-effects were reported for either treatment noted. These results suggest that RRE can reduce general fatigue under certain stressful conditions.

Key words: *Rhodiola rosea* L., fatigue, anti-fatigue effect, non-pathological stress, working conditions, adaptogen, standardized extract SHR/5.

Introduction

Rhodiola rosea L. is a medicinal plant from the *Crassulaceae* family, with the main active substance salidroside, a phenylpropanoide (Steinegger-Hänsel, 1992, Saratikov et al., 1968). *Rhodiola rosea* is grown in dry and sandy ground, mainly in the Arctic and Alpine regions of Europe, Asia and America. The part used in medicine is the root-stock, while the green aerial part is used as a food ingredient. *Rhodiola* has a long tradition as a medicinal plant in several European countries, notably Iceland (Hjaltalin, 1830; Hallgrímsson, 1964), Norway (Hoeg, 1984), Sweden (Roselli, 1755; Sandberg and Hansen, 1998; Sandberg and Bohlin, 1993), France (Pharmacopée Française, 1974), Greece and Russia. Its use in the medicine was reflected already in the first Swedish Pharmacopoeia (Pharmacopoeia Svecia, 1775) and Materia Medica (Materia Medica, Linnaei, 1749) and appears also more recently in the French Pharmacopoeia (1974) as well as in the Estonian (Estonian Ministry of Health, 1998).

In Europe the use of *Rhodiola rosea* L. in medicine dates back to the ancient Greeks (Mell, 1938). Dioscorides referred to it in the 1st century A.D., under

0944-7113/00/07/05–365 $ 15.00/0

the name of *Rodia riza*. In England and on the continent, the drug became known as lignum rhodium in apothecary shops. It was Linnaeus who gave the plant its botanical name *Rhodiola* and its species name, *rosea*. The name alludes to the rose-like odor of the rootstock when freshly cut. In France Rhodiola was used as „brain tonic" in the early 19th century (Virey, 1811) and in the alpine region of Germany against headache (Strigl, 1928).

In Russia, *Rhodiola rosea* has been used traditionally and pharmacologically for a long period of time (Saratikov, 1966). *Rhodiola rosea* L. (RRE) preparations have also been used extensively in traditional Tibetan medicine since 300 A.D. for treating lung diseases, particularly lung-heat disorders (Tsarong, 1986; Li, 1995). Thus, among the 175 most important Tibetan drugs in the Handbook of Traditional Tibetan Drugs, *Rhodiola* is mentioned in ten formulations, of which nine are indicated for lung disorders (Tsarong, 1986).

It is, however, primarily in Russia and former USSR that preparations based on *Rhodiola rosea* rhizome and the glycoside salidroside (synonym: rhodioloside, rhodosine) have gained an established position and use within the official medicine (Muravijeva, 1978, Mashkovskij, 1977, Turova and Sapozhnikova, 1984).

The use in medicine in the former USSR/Russia, goes back to a number of pharmacological and clinical investigations in the early 1960, which demonstrated primarily stimulant and anti-stress actions (Müller-Dietz, 1970; Saratikov, 1974). As a result of these studies, preparations based on *Rhodiola rosea* became incorporated into the officinal medicine by 1969 and are described in the last official USSR/Russian Pharmacopoeia and in the current Russian Pharmacopoeia (National Pharmacopoeia of the USSR, 11th Edition, 1987; National Pharmacopoeia Committee, 1996).

The stimulant and anti-stress actions of *Rhodiola rosea* and its active component salidroside (synonym: rhodioloside) have been studied extensively in the USSR/Russia (Aksyonova, 1966, Saratikov, 1974, Sokolov, et al., 1985). A bibliography of published scientific reports on *Rhodiola rosea* (and salidroside) from 1961 to 1987 contains 321 references, of which 119 are pharmacological and clinical studies (Saratikov, 1988).

Pharmacologically, *Rhodiola rosea* and its main active component, salidroside has pronounced and well-documented stimulant and adaptogenic action (Wagner et al., 1994; Brekhman and Dardymov, 1969; Saratikov et al., 1968; Nörr, 1993; Petkov et al., 1986). The stimulant effect is a part of the adaptogenic action (Saratikov et al., 1965: Zotova, 1966: Saratikov, 1974: Saratikov et al., 1978: Marina and Mikhaleva, 1987). Adaptogenic action is a pharmacological effect seen in clinical studies as an increased resistance to the harmful effects of various stressors.

It has been shown in pharmacological investigations that *Rhodiola rosea* extracts (RRE) protect laboratory animals from the harmful effects of oxygen, cold, radiation and heavy physical exercise (Saratikov et al., 1968). The stimulant effect of *Rhodiola rosea* increases working capacity, tolerance to anoxia, resistance to microwave irradiation and poisoning by toxins. It decreases also fatigue and regulates brain function (Azizov and Seifulla, 1998, Saratikov et al., 1968). Rats treated with *Rhodiola rosea* extract (RRE) showed improved learning behavior in a maze model 24 hours after treatment. Significant improvement of long-term memory has also been established using memory tests after 10 days' treatment (Petkov et al., 1986).

Human studies have shown that salidroside, an active principle of *Rhodiola*, improved mental ability. In correction tests, the error rates were reduced by approximately fifty persent (Wagner et al., 1994). For a more detailed discussion see Brekhman, Dardymov and Nörr (Brekhman and Dardymov, 1969; Nörr, 1993; Wagner et al., 1994; Fulder, 1980).

An overview of the clinical studies of the anti-fatigue effect of *Rhodiola rosea* preparations shows that a majority are based on single-dose application with a significant effect after 1–2 h. This observation was one of the main motivations for performing a clinical study with repeated dose application of a low daily dose. Another important consideration was to make the investigation in a nearly realistic work situation.

The aim of this placebo-controlled, double-blind cross-over study was to evaluate the efficacy of a *Rhodiola rosea* extract (RRE) with standardized content of salidroside. The study was performed as treatment of non-specific fatigue, resulting from natural physical fatigue and using quantitative analysis of speed of audio-visual perception and short-term memory as criteria for fatigue. The study was based on a model reflecting common work conditions.

Material and Methods

The study was performed in compliance with the revised declaration of Helsinki and approved by the Ethical Review Committee of the Armenian State Medical University of Yerevan.

- *Study design:* The clinical investigation was carried out as a randomized, placebo-controlled, double-blind, cross-over study with a wash-out period. The study was intended to investigate the efficacy of a standardized extract SHR/5 from *Rhodiola rosea* rhizome (RRE) in non-specific fatigue. The primary objective was to study the anti-fatigue effect of *Rhodiola rosea*

preparation using repeated low-dose regimen in healthy volunteers during work-related fatigue. The study parameter chosen and considered relevant for assessment was the degree of fatigue, based on the evaluation of audial and visual short-term memory and ability for mental attention. The level of non-specific fatigue after the night duties was evaluated using five tests focused on the determination of speed of visual and audial perception, attention capacity and short-term memory. These tests were as follows:

Test 1: the speed of determination of words associated by meanings, scored in seconds.
Test 2: the speed of backward spelling of a 6-letter word, scored in seconds.
Test 3: the speed of subtraction of a given digit sequentially as far as possible from a number between 90 and 99 to 0, scored in seconds.
Test 4: the number of correctly recalled words, irrespective of sequence and with no time-limit, ten of which were presented audially to the subject, scored in numbers.
Test 5: the speed of rearranging digits into an order of decreasing magnitude. The digits were randomly distributed in a square, scored in seconds.

For explanation of the rationale for using this test-battery in the measurement of non-pathological fatigue, see MacKinnon and Yudofsky (1986).

A fatigue index was calculated based on these parameters. As a measure for fatigue, each test was given a measure, an index, defined as the following ratio: (score of test before night duty divided by score of test after night duty) x 100. Five different measurements were assessed collectively, giving a total fatigue. The total effect of taking RRE was assessed according to the total fatigue index, FI, which directly gives the level of performances after duty on each occasion in percent of the performance before duty. Each subject was randomly assigned the medication form two directed sets of jars, containing Clinical A 971106 or Clinical B 971106. The volunteers were, according to the assignment of test medication, divided into two groups, A and B. During the first two weeks, the group A (26 persons) each received 1 tablet from the Clinical A batch per day, while group B (30 volunteers) each received 1 tablet from the Clinical B batch per day. During the following two weeks of wash-out period no participants received any medication. After that, both groups were again on two weeks of medication with the opposite clinical batch.

Determination of the level of fatigue after night duty was conducted on the basis of test results before and after duty, i.e., with a time difference of 24 hours.

Each volunteer was tested before receiving the preparation or placebo, at the end of the 2-week period of taking the preparation, at the end of the two weeks wash-out period and at the end of the two weeks of cross over period. For each test occasion, all the scorings for tests 1–5 were tabulated and used as ranking data for a subsequent statistical analysis of all the tests taken together, see Table 1.

Selection of patients. The patients were recruited according to specified inclusion and exclusion criteria after having received written and verbal information about the Department of Neurology, Armenian State Medical University of Yerevan. The patients were comprised of young, healthy physicians on night duty, chosen by Dr. V. Darbinyan and Dr. A. Kteyan during January 1998 – March 1999. All participants were residents of Armenia and had a similar socio-cultural background.

Patient inclusion criteria

1. Age between 24–35, of both genders.
2. Compliance with the study specifications.
3. All patients were informed about the study and a written consent was requested.

Patient exclusion criteria

1. Mental disease or declared psychological or major emotional problems.
2. Somatic disease or complaint with fatigue as a symptom.
3. Other medication

Study medication. The test medication (verum and

Table 1

	Test occasion no. I	II	III	IV
Group A	Before receiving RRE	After two weeks of receiving RRE	After two weeks of wash-out period without any perparation	After two weeks of receiving placebo
Group B	Before receiving placebo	After two weeks of receiving placebo	After two weeks of wash-out period without any preparation	After two weeks of receiving RRE

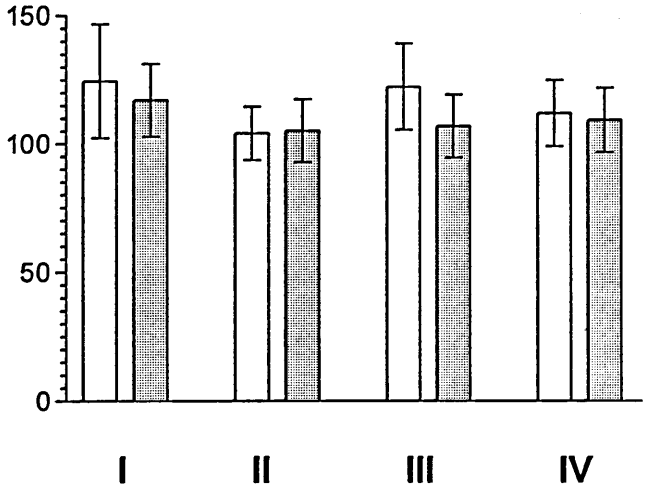

Fig. 1. Mean values of Fatigue indices and total index. (Value of scoring before duty = 100).

placebo) was manufactured according to Good Manufacturing Practice (GMP) by Swedish Herbal Institute (SHI) in the form of white, sugar-coated tablets, with the following composition: *VERUM TABLETS*, Extr. sicc. *Rhodiola rosea* SHR/5 170 mg (containing approximately 4.5 mg salidroside), calcii phosphas dibasicus, solani amylum, cellulosum microcristallinum, magnesii stearas, silica colloidalis anh.; *PLACEBO TABLETS*, Lactose 170 mg, calcii phosphas dibasicus, solani amylum, cellulosum microcristallinum, magnesii stearas, silica colloidalis anh.; *COATING FOR BOTH VERUM/PLACEBO*, Saccharose, calcium carbohydrate, magnesium silicate, polyvinylpyrrolidone, titan dioxide.

Verum and placebo tablets were produced with identical organoleptic appearance, and were indistinguishable from each other. Each package of tablets contained 60 tablets to be taken once daily for 14 days. The medications were divided into two sets of plastic jars which were labelled: Clinical A 971106 and Clinical B 971106. An identification number was noted in a protocol to allow a subsequent identification after the completion of the study and statistical analysis. The information on the placebo and the active substance became available to the investigators and volunteers only after the completion of the study and after the statistical analysis was performed.

Table 2

	Group A		Group B	
Total fatigue index	I – II	III – IV	I – II	III – IV
Student's T-test P-value	0.003 (n.s)	0.2 (n.s.)	0.08 (n.s.)	0.5

Anthropometric Data

Group A: 26 persons: 14 females, 12 males, age 25.5 ± 3.8.

Table 3. Test scores: Mean values and standard deviations.

			PERIOD							
			I		II		III		IV	
Group	Test	B/A	Mean v.	Std	Mean v.	Std	Mean v.	Std	Mean v.	Std
A	1	Before	108.98	31.7	85.5	22.0	90.5	23.2	96.2	22.4
A	1	After	135.8	48.5	86.5	26.0	111.9	40.7	110.1	32.4
A	2	Before	8.5	4.1	7.3	2.7	7.9	4.1	7.7	3.7
A	2	After	11.5	5.3	7.7	2.5	10.5	5.9	8.9	4.1
A	3	Before	34.5	12.1	33.2	12.4	35.4	12.9	43.2	22.0
A	3	After	40.8	19.8	28.9	9.3	41.8	18.3	49.1	23.3
A	4	Before	7.7	1.1	7.3	1.2	6.9	1.4	8.2	0.9
A	4	After	6.7	1.7	6.7	1.6	6.2	1.9	8.0	1.1
A	5	Before	65.4	19.4	77.5	27.9	72.3	24.5	68.4	20.7
A	5	After	72.7	20.1	80.0	35.9	83.6	30.5	72.5	28.0
B	1	Before	96.0	21.8	91.3	20.0	89.3	14.3	95.3	14.8
B	1	After	120.1	35.1	91.7	20.7	91.9	14.7	96.3	17.4
B	2	Before	8.8	2.5	8.6	2.9	8.4	3.1	8.3	2.6
B	2	After	11.2	3.6	10.3	3.7	8.8	3.3	8.9	3.4
B	3	Before	40.9	8.5	42.0	9.9	42.7	10.1	43.6	11.8
B	3	After	44.0	9.7	41.6	9.9	41.0	8.5	44.4	10.3
B	4	Before	7.4	1.3	7.9	1.6	8.1	1.4	8.0	1.2
B	4	After	7.1	2.2	7.8	1.8	8.1	1.5	7.1	1.4
B	5	Before	68.1	22.3	105.8	48.6	76.0	27.2	62.3	14.4
B	5	After	72.3	15.9	90.7	33.4	86.4	29.2	70.5	18.5

Group B: 30 persons: 19 females, 11 males, age 27.3 ± 2.9.

Statistical analysis. Statistical analysis of the total fatigue indices was performed according to the Student's T-test, two-tailed. Data management and calculations were performed using PRISM Statistical Software Version 2.01 (1996).

Results and discussion

All the patients completed the study and no adverse effects or events were observed. As presented in Figure 1 and Table 2, total fatigue index was significantly improved after two weeks of taking the RRE preparation.

In different clinical trials with *Rhodiola rosea* products, psycho-stimulating, tranquilizing and antidepressive effects have been demonstrated. The preparation is also used for correction of aesthenic conditions (Mikhailova, 1983). A few clinical studies are also worth noting. Studies have been completed with RRE in psychiatric practice as an adjuvant anti-depressant (Brichenko et al, 1986) and as an anti-depressant (Brichenko and Skarokhodova, 1987). The anti-hypnotic effect of the active substance was assessed by Aksenova (Aksenova et al., 1968). Komar studied the stimulating effect in 254 young healthy persons, demonstrating an increased mental work capacity after intake of a *Rhodiola rosea* preparation (Komar et al., 1981). Several other similar studies were made by a number of investigators (Saratikov, 1974; Krasik et al., 1970a; Krasik et al., 1970b; Lapaev, 1982; Metscheryakova et al., 1975; Oleinichenko, 1966; Tuzov, 1968; Mikhailova, 1983).

The use of adaptogens against common non-pathological stress under normal conditions of usual working activity could be of great practical significance. The challenges in the experimental data in clinical practice are the methodological difficulties in measuring such a subjective and complex notion as fatigue. The advantage of the chosen model in a common working situation causing fatigue were the similarity of the stress situation for all the participants in an actual and realistic work situation. Regular night duty work is well known to be stressful and to play a part in causing various pathological conditions, such as long term disturbances of sleep and depressions (Czeisler and Richardson, 1998).

Table 3 presents the mean values of the actual score for each test and period. As is seen, the absolute values of the scores vary considerably from test to test.

To be able to directly compare the tests, Table 4, presents the more relevant relative measure called Fatigue index as defined above. The fatigue index subtracted by 100 (FI – 100) gives directly the change in percent of the performance before and after duty.

The difference between the tests as a measure of fatigue is directly seen from this table. As an example, appears test 1 to be more sensitively dependent on the state of fatigue than test 4, as appears directly from the larger magnitude of a fatigue indices. To have a more relevant and also more reliable measure of the degree of fatigue a total fatigue index was calculated, using the fatigue indices from each test with equal weight. The result is displayed in Table 2 and in Figure 1. The only significant change is seen in the verum group between period I and period II with a change in performance of approximately 20 % ($p < 0.01$). Furthermore this study also shows that for the chosen dosage there was no efficacy in group B after six weeks of treatment. On the second test occasion however, the subjects had been on night duty for a considerably longer time than for the first occasion. It should therefore be taken into consideration that the low dosage used was well-adapted for

Table 4. Mean values of Fatigue indices and total fatigue index. (Value of scoring before duty = 100)

		PERIOD I		II		III		IV	
Test	Group	Mean v.	Std	Mean v.	Std	Mean v.	Std	Mean v.	Std
1	A	125.8	38.5	101.4	17.5	124.0	36.7	115.9	28.5
1	B	124.6	21.4	101.1	13.2	103.4	10.0	101.0	9.5
2	A	144.3	56.4	113.3	34.6	136.3	39.9	118.0	32.9
2	B	127.8	30.3	121.6	37.6	107.4	23.1	108.6	32.2
3	A	117.4	32.8	89.9	17.3	118.7	28.2	115.1	24.3
3	B	108.3	15.1	99.8	12.9	97.0	10.2	103.2	13.1
4	A	116.0	17.6	108.0	19.5	111.0	16.0	102.0	15.3
4	B	105.0	21.0	100.0	17.8	101.0	16.5	112.0	15.0
5	A	113.3	21.6	102.5	19.8	116.8	20.7	105.9	17.8
5	B	114.1	35.0	99.1	45.5	126.1	59.2	116.2	32.0
Tot. fat. ind.	A	124.5	22.2	104.0	10.5	122.2	16.8	111.9	13.0
Tot. fat. ind.	B	117.0	14.2	105.1	12.3	106.8	12.4	109.2	12.6

Table 5. Correlation between before-duty scores on occasion I and III.

Test	Group	Pearson's test	P-value
1	A	0.48	0.013
1	B	0.503	0.005
1	A + B	0.481	0.0002
2	A	0.493	0.01
2	B	0.486	0.006
2	A + B	0.47	0.0003
3	A	0.588	0.002
3	B	0.685	0.0001
3	A + B	0.66	0.0001
4	A	0.125	0.54
4	B	0.54	0.003
4	A + B	0.266	0.049
5	A	0.362	0.075
5	B	0.072	0.712
5	A + B	0.193	0.16

the situation on the first occasion but not sufficient on the second occasion. It can, however, be concluded that *Rhodiola rosea* SHR/5 extract possesses a clear anti-fatigue effect without any reported adverse reactions or side-effects, at the dosage used in our study in a situation of a moderate level of fatigue and stress.

To shed some more light on the asymmetry of the results between occasion I and II versus III and IV some further questions could be asked:

A basic assumption in cross-over studies is that each individual is in a very similar state on occasion I and after a wash-out period on occasion III. To examine if this assumption holds, the correlation between the before-values on occasion I and on occasion III was calculated. The results are presented in Table 5. The most conspicuous feature is the difference in degree of correlation between tests 1, 2 and 3 versus 4 and 5. While 1, 2 and 3 exhibit a rather good correlation, test 4 and 5 show poor correlation between occasion I and III. This calls for a closer look at these two groups of tests.

First of all, the mean values of the test scores (before values) on occasion I and III do not display a learning effect to which the difference between the two groups of tests could be attributed. Secondly, there does not seem to be an inherent difference in the kind of test between the two groups. However, test 4 differs from all the others in the sense that there is no time limit. On the other hand test 5, showing the lowest correlation does not exhibit any easily distinguishing characteristic. To sum up: Judging from the mean values of the before duty scores, the important assumption of basic similarity between occasion I and occasion III could not be said to hold to a satisfying degree. Test 4 and 5 are responsible for the largest variation but no immediate reason for this could be seen.

The size of the study does not allow for further general conclusions but surely suggests that in a future study of similar design, both higher doses and a larger number of subjects should be used. The present study also indicates that another choice of the test battery, could be more sensitive in assessing a general state of fatigue.

References

Aksenova, R.A., Zotova, M.I., Nekhoda, M.F., Cherdantsev S.G.: „Comparative characteristics of the stimulating and adaptogenic effects of *Rhodiola rosea* preparations", in: *Stimulants of the CNS*, *Tomsk 2:* 3–12, 1968.

Aksyonova. R.A.: „The stimulating and adaptogenic effect of a purified *Rhodiola rosea* preparation – rhodosine", in: *Stimulants of the Central Nervous System*, Tomsk, pp. 77–79, 1966.

Azizov, A.P., Seifulla, R.D.: The effect of Elton, Leveeton, Phytoton, and Adapton on the working capacity of experimental animals. *Eksp. Klin.Farmakol. 61(3):* 61–63, 1998.

Brekhman, I.I., Dardymov, I.V.: New substances of plant origin which increase non-specific resistance. *Ann. Rev. Pharmacol. 9:* 419–430, 1969.

Brichenko, V.S., Kupriyanova, I.E., Skorokhodova, T.F.: „The use of herbal adaptogens together with tricyclic antidepressants in patients with psychogenic depressions", in*: Modern Problems of Pharmacology and search for new Medicines, Tomsk, 2:* 58–60, 1986.

Brichenko, V.S., Skorokhodova, T.F.: Herbal Adaptogens in Rehabilitation of Patients with depression, Clinical and Organisational Aspects of early Manifestations of Nervous and Mental diseases, Barnaul, p. 15, 1987.

Czeisler, C.A., Richardson, G.S.: „Disorders of sleep and circadian rhythms", in: *Harrison's 14 CD-ROM*, McGraw-Hill, 1998.

Estonian Ministry of Health Affairs, 21st January, Regulation No. 7, annex 1, 1998.

Fulder, S.: The drug that builds Russians. *New Scientists 21:* 576–579, 1980.

Hallgrímsson, H.: *De Rhodiolae, Flóra,* 77–87, 1964.

Hjaltalin, J.: *Botany of Iceland*, Oslo, 237, 1830.

Hoeg, O.A.: *Våre Medicinske Planter*, Det Beste, Oslo, 237, 1984.

Komar, V.V., Kit, S.M., Sishchuk, L.V., Sishchuk, V.M.: Effect *of Rhodiola rosea* on the human mental activity. *Pharmaceutical J. 36:* 4:62–64, 1981.

Krasik, Ye.D., Morozova, E.S., Petrova, K.P., Rogulina, G.A., Shemetova, L.Ya., Shuvayeva.: New data on the therapy of asthenic conditions (Clinical prospects for the use of *Rhodiola* extract). Material for All-Russia Conf.: *Urgent Problem in Psychopharmacology,* 298–300, 1970a.

Krasik, Ye.D., Petrova, K.P., Rogulina, G.A.: About the adaptogenic and stimulating effect of *Rhodiola rosea* extract, Materials of All-Union and 5th

Sverdlovsk Area Conf. of Neuropathologists, Psychiatrists and Neurosurgeons, 26–29 May, proceedings, 215–217, 1970b.

Lapaev, I.I.: „The effect of herbal adaptogens in working capacity of sportsmen-divers“, in: *Modern Problems of Military Medicine, Tomsk, 2:* 173–175, 1982.

Li Y.: The characteristics of Tibetan medicine preparation in Sibu Yidian [Tibetan Medical Dictionary], *Chinese Journal of Ethnomedicine and Ethnopharmacy, 14:* 16–19, 1995.

MacKinnon, R.A., Yudofsky, S.C.: „Methodology of psychiatric evaluation“, in: *Principles of the psychiatric evaluation. J.B. Lipincott Co.,* New York, London, 241–248, 1986.

Marina, T.F., Mikhaleva, L.K.: „Comparative characteristics of the effect of Para-Tyrosol and *Rhodiola* extract upon the higher nervous activity in rats“, in: *Stimulants of the Nervous System,* pp. 16–19, 1987.

Mashkovskij, M.D.: Medicines (Manual on Pharmaco-therapy for doctors) Part I, Eight revised and amended, Publ. Meditsina, Moscow, 133, 1977.

Materia Medica, Linné, C, Liber I. de Plantis, 168, 1749.

Mell, C.D.: Dyes, tannins, perfumes and medicines from *Rhodiola rosea*. *Textile Colorist 60:* 715: 483–484, 1938.

Metscheryakova, E.I., Mikhailova, M.N., Abrameitsev, V.D.: A study of *Rhodiola rosea* extract effect using the MMPI method. Material of Sci. Pract. Conf. Problems of Rehabilitation of patients with nervous and mental diseases, *Tomsk University Press,* 180–182, 1975.

Mikhailova, M.N: „Clinical and experimental substantiation of asthenic conditions therapy using *Rhodiola Rosea* extract“ in: *Current Problems of Psychiatry*, *Tomsk,* 126–127, 1983.

Muravijeva, D.A.: Pharmacognosy (With fundamentals of biochemistry of medicinal herbs), Publisher Meditsina, 541 –546, 1978.

Müller-Dietz, H.: Arzneipflanzen der Sowietunion, Book, Freien Universität, 91–92, 1970.

National Pharmacopeia Committee, Pharmacopoeia article; PA 42–2163-96, Extractum Rhodiolae fluidum, The Russian Federation Ministry of Health and Medical Industry, 1996.

National Pharmacopoeia of the USSR, 11th ed., part I, 1987, *Rhodiola rosea* rhizome and roots, pp. 364–366, 1987. New printing 1:2 Moscow, 1998.

Nörr, H.: Phytochemical and Pharmacological Investigation of the Adaptogenes: *Eleutherococcus senticosus*, *Ocimum sanctum, Codonopsis pilosula*, *Rhodiola crenulata*. Ph.D. Dissertation, Faculty of Chemistry and Pharmacy, Ludwig-Maximillians University, Muenchen, 228 pages, 1993.

Oleinichenko, U.F.: „The effect of *Eleutherococcus* and *Rhodiola rosea* extracts upon the functional condition of the organ of hearing in those working in noisy shops of the Tomsk Electric engineering plant and in pilots of the Tomsk Airport“, in: *Stimulants of the Central Nervous System*, 124–127, 1966.

Pharmacopée Française, IX edition, 214/100, 1974.

Petkov, V.D., Yonkov, D., Mosharoff, A., Kambourova,T., Alova, L., Petkov, V.V., Todorov, I.: Effects of alcohol aqueous extract from *Rhodiola rosea* L. roots on learning and memory. *Acta Physiol. Pharmacol. Bulg. 12(1):* 3–16, 1986.

Pharmacopoeia Svecia, Holmia, 39, 1775.

Roselli, C.: En liten dock mycket nyttig örtabok eller Den lille Naturläkaren, book, C. Topelius, 1755 (Facsimile C. Topelius, 1974).

Sandberg, F., Bohlin, L.: Fytoterapi – växtbaserade läkemedel, Hälsokostrådets förlag, 131, 1993.

Sandberg, F., Hansen, H.A.: „Örtmedicin och växtmagi, Publishing house: Reader‘s Digests AB, Stockholm, 233, 1998.

Saratikov, A.S.: Some results in the search and study of herbal stimulants of the central nervous system, The CNS stimulants, Tomsk University Press, 3–23, 1966.

Saratikov, A.S.: „Chapter VII: Clinical studies on *Rhodiola rosea*“, in: *Golden Root*, Tomsk University Publishing House, 131–139, 1974.

Saratikov, A.S.: „Bibliography on Rhodiola rosea 1961–1988“, in*: Golden Root – Rhodiola rosea*, Tomsk University Press. 1988.

Saratikov, A.S.; Marina, T.F.; Fisanova, L.L.: „On the effect of salidroside on turnover of catecholamines in brain“, in: *Biologicheskiye Nauki 6:* 142,1978.

Saratikov, A.S., Marina, T.F., Kaliko, I.M.: The stimulating effect of *Rhodiola rosea* on the higher brain structures. *Newsletter of the Siberian Branch of the USSR Academy of Science 8 (Biology 2):* 120–125, 1965.

Saratikov, A.S., Krasnov, E.E., Chnikina, L.A., Duvidson, L.M., Sotova, M.I., Marina, T.F., Nechoda, M.F., Aksenova, R.A., Tschrdinzeff, S.G.: „Rhodiolosid ein neues Glykosid aus *Rhodiola rosea* und seine pharmakologischen Eigenschaften“, in: *Die Pharmazie 23:* 392–395, 1968.

Sokolov, S.Ya., Ivashin, V.K., Zapesochnaya, G.G., Kurkin, V.A., Shchavlinskii, A.N.: Studies of neurotropic activity of new compounds isolated from *Rhodiola rosea* L. *Clinical Pharmaceutical J. 19, 11:* 1367–1371, 1985.

Steinegger-Hänsel: Pharmakognosie, 5. ed. Springer-Verlag, HeidelbergAuflage, 613, 1992.

Strigl von, J.: Arzneimittel der Vergangenheit. Druck Aloys Gogeissl, Passau, 22, 1928.

Tsarong, T.J.: Handbook of Traditional Tibetan Drugs, Tibetan Medical Publications, Kalimpong, India, 1986.

Turova, A.D., Sapozhnikova, E.N.: Medicinal Plants of the USSR and Their Use, Fourth edition, Moscow, Publisher Meditsina, 35–37, 1984.

Tuzov, S.F.: „Comparative characteristics of the effect of some CNS stimulants on muscular capacity on men“, in*: Stimulants of the CNS, Tomsk, 2:* 156–161, 1968.

Wagner, H., Nörr, H., Winterhoff, H.: Plant Adaptogens. *Phytomedicine 1:* 63–76, 1994.

Virey, J.-J.: Traité de pharmacie théorique et pratique. Paris, 92, 1811.

Zotova, M.I.: „A comparative characteristic of the stimulating and adaptogenic effect of *Rhodiola rosea* and *Eleutherococcus* extracts“, in: *Stimulants of the Central Nervous System*, *Tomsk*, 67–71, 1966.

Address

Vahagn Darbinyan, Department of Neurology, Institute of Surgery, Armenian Medical University, 9 Asratyan St., Kanaker Yerevan, Armenia 375000.
Tel. +0 (3742) 284 401 E-mail: epilepsy@acc.am

Book Review

Loew, D. Rietbrock, N. (Eds); **Phytopharmaka I-IV. Forschung und Klinische Anwendung**. Steinkopf Verlag, Darmstadt.
Volume I: 198 pp, 1995. ISBN 3-7985-1053-9;
Volume II: 210 pp, 1996. ISBN 3-7985-1066-0;
Volume III: 215 pp, 1997. ISBN 3-7985-1094-6;
Volume IV: 186 pp, 1998. ISBN 3-7985-1131-4.

Loew, D. Blume, H. and Dingermann Th. (Eds.); **Phytopharmaka V. Forschung und Klinische Anwendung**, 226 pp, Steinkopf-Verlag, Darmstadt, 1999. ISBN 3-7985-1203-5.
Price: All volumes DM 68; öS 496,40; sFr 60.

The five volumes published up to now contain the lectures presented at the annual phytomedicine symposia of the German Society for Clinical Pharmacology. The aim of these symposia is to review the most current therapeutic status of rational herbal medicinal products (HMP). HMPs are subjected to the same scientific requirements concerning efficacy, safety and quality as those applied to synthetic drugs.

Today therapy with HMP is a definite component of traditional medicine, which is subject to the rules of controlled clinical studies according to the guidelines of good clinical practice. It clearly needs to be differentiated from the numerous methods of so called alternative medicine.

For a number of years HMPs have been placed in an area of conflict between a tradition of several centuries and a Evidence Based Medicine (EBM). EBM perceives itself as a quality-orientated but not as a view-orientated implementation of scientific knowledge, and derives concrete therapeutic recommendations from a five-level hierarchy of evidence. Though EBM seems to present itself as a rational and pragmatic procedure for decision-making, from an optimal pharmaco-economically orientated medical support, criticism arises from the fact that therapeutic experience and the requirements of daily practice are not considered in EBM.

The subjects treated in the symposia proceedings concern the clinical-pharmacological basis of the efficacy of HMP (e.g., metabolism of multi-drug-mixtures, analysis and bioequivalence-investigations of HMP), toxicological and safety aspects (mutagenicity and carcinogenicity studies), the pharmaceutical characterization of HMP (e.g., selection of drugs and drug quality, industrial quality control, biopharmaceutical quality and problems of equivalence of HMP), Evidence Based Medicine and clinical application (e.g., anxiety states, diseases of the respiratory tract, dementia, depressive states, gynecological diseases, cardiac insufficiency, immune deficiency, cancer, benign prostatic hyperplasia, venous diseases, application of HMP in pediatrics, and use of HMP in self medication).

The scope of herbal drugs which have been subject to pharmacological and clinical studies includes preparations from *Aesculus hippocastanum*, Anthranoid-drugs, *Cimicifuga racemosa, Crataegus spp, Cucurbita pepo, Ginkgo biloba, Cynara scolymus, Echinacea spp, Harpagophytum procumbens, Hypericum perforatum, Mentha piperita, Piper methysticum, Plantago lanceolata, Sabal serrulata, Senna spp, Silybum marianum, Urtica spp., Viscum album, Vitex agnus castus* as well as ß-Aescin, volatile oils, silibinin and silymarin.

The results of pharmacological and clinical trials, presented in the first five volumes of Phytopharmaka, make clear that rational HMP is taking an essential place in medicinal therapy and can meet the requirements of the evidence-based hierarchy from the standpoint of quality, clinical trials and meta analyses. The books represent an essential basis for all scientists concerned with herbal medicinal products in research, clinic and practice.

H. D. Reuter
Gesellschaft für Phytotherapie e.V.
Siebengebirgsallee 24
50939 Köln