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ARTICLE *in* NORDIC JOURNAL OF PSYCHIATRY · FEBRUARY 2007

Impact Factor: 1.34 · DOI: 10.1080/08039480701643290 · Source: PubMed

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Darbinyan V, Aslanyan G, Amroyan E, Gabrielyan E, Malmström C, Panossian A. Clinical trial of *Rhodiola rosea* L. extract SHR-5 in the treatment of mild to moderate depression. Nord J Psychiatry 2007;61:343–348. Oslo. ISSN 0803-9488.

The objective of this study was to assess the efficacy and safety of standardized extract SHR-5 of rhizomes of *Rhodiola rosea* L. in patients suffering from a current episode of mild/moderate depression. The phase III clinical trial was carried out as a randomized double-blind placebo-controlled study with parallel groups over 6 weeks. Participants, males and females aged 18–70 years, were selected according to DSM-IV diagnostic criteria for depression, the severity of which was determined by scores gained in Beck Depression Inventory and Hamilton Rating Scale for Depression (HAMD) questionnaires. Patients with initial HAMD scores between 21 and 31 were randomized into three groups, one of which (group A: 31 patients) received two tablets daily of SHR-5 (340 mg/day), a second (group B: 29 patients) received two tablets twice per day of SHR-5 (680 mg/day), and a third (group C: 29 patients) received two placebo tablets daily. The efficacy of SHR-5 extract with respect to depressive complaints was assessed on days 0 and 42 of the study period from total and specific subgroup HAMD scores. For individuals in groups A and B, overall depression, together with insomnia, emotional instability and somatization, but not self-esteem, improved significantly following medication, whilst the placebo group did not show such improvements. No serious side-effects were reported in any of the groups A–C. It is concluded that the standardized extract SHR-5 shows anti-depressive potency in patients with mild to moderate depression when administered in dosages of either 340 or 680 mg/day over a 6-week period.

• *Adaptogens*, Rhodiola rosea, *Depression*, *Placebo-controlled trial*, *Double-blind parallel-group trial*.

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Depressive symptoms are not only disabling but are also very common. It is estimated that around 10% of the adult population suffer from such disorders, although some studies indicate that the true figure may be higher. Typically, mild to moderate depression presents itself in the form of mood disturbance, lack of mental energy, sleep disturbance, low self-esteem and a wide variety of somatic complaints. In those cases that do not present serious melancholy or suicidal risk, it would be preferable to treat the disorder with anti-depressive medications that do not exhibit any of the disturbing side-effects associated with the standard drugs, such as tricyclic anti-depressants, selective serotonin or noradrenaline reuptake inhibitors (1–3).

Rhodiola rosea L. is a well-known adaptogen that induces a state of non-specific resistance to damaging effects of various stressors (4–6). Previously, it has been demonstrated that when an extract of *R. rosea* is administered together with tricyclic anti-depressants there is a marked reduction in the side-effects of the drugs and a positive effect on psychopathological symptoms in patients with psychogenic depression (7, 8). However, we have not been able to find any publications concerning the clinical trial of the anti-depressive effect of mono-therapy with *R. rosea*.

The aim of the present study was to investigate the direct anti-depressive effect of SHR-5, a standardized extract of *R. rosea* rhizome, in patients suffering from mild to moderate depression. A double-blind, placebo-controlled, randomized phase III pilot study was carried out in order to determine the therapeutic efficacy and safety of SHR-5 extract compared with placebo.

 DOI: 10.1080/08039480701643290

The relationship between different doses of the adaptogen (340 and 680 mg/day of extract per day) and their anti-depressant efficacy compared with placebo were examined.

Material and Methods

Study protocols were submitted to and approved by the Ethics Committee of the Armenian Drug and Medical Technology Agency of the Ministry of Health of the Republic of Armenia. Studies were performed in compliance with the revised declaration of Helsinki (9) and written informed consent was obtained from all participants.

Study drugs

All test medications were manufactured according to Good Manufacturing Practice (GMP) by the Swedish Herbal Institute (SHI: Gothenburg, Sweden) and presented in the form of white tablets coated with sugar. The verum tablets (400 mg) each contained 170 mg of *Rhodiola* extract SHR-5. Placebo tablets (400 mg) were prepared using the inactive ingredients that were identical to verum tablets except 170 mg of lactose. Verum and placebo tablets were identical in appearance and organoleptic properties. Individual medication packs were provided to subjects in the form of plastic jars containing 100 tablets and bearing a code number (randomly encoded in a drug list) on a label that was designed in accordance with the valid guidelines for Good Clinical Practice (GCP). In addition to the main label, each jar had a small supplementary label with information on dosage regimen (two or four) were to be taken daily. Duplicate jars, each containing 100 tablets, were provided to those patients required to take four tablets daily.

The code was broken after completion of the study and after statistical analyses had been performed.

Study design

The investigation was a double-blind, randomized, parallel-group evaluation of SHR-5 extract vs. placebo. Male and female subjects, aged between 18 and 70 years and diagnosed with mild or moderate depression according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria (10), attending the in- or outpatients sections of the Erebouni Medical Center, Department of Neurology, Armenian State Medical University, Yerevan, Armenia, were considered for inclusion in the study. Since eligible individuals were required to have clinically significant depression, only patients with initial scores of $\geq$13 on the Beck Depression Inventory (BDI: 13-item short form) and of $\geq$21 on the Hamilton Rating Scale for Depression (HAMD; 21-item version) (11–13) were selected. The BDI and HAMD tests were performed by skilled physicians using Armenian and Russian language versions of the questionnaires as appropriate in order to avoid possible misinterpretations.

Subjects were excluded from the study if: 1) there was evidence of a previously documented or reported attempt to commit suicide, 2) if they scored $\geq$1 on BDI item H or $\geq$2 on HAMD item 3 (suicidal tendency), 3) if they presented a total HAMD score above 31, 4) if they presented progressive organic or metabolic brain syndrome, or compulsive, schizophrenic or other delusive disorders, or 5) if they were pregnant or lactating. Patients suffering from, and/or receiving medication for serious chronic illnesses (including cardiovascular diseases and diabetes) were also excluded because of the possibility of drug interactions.

Prior to the commencement of the study, all included subjects underwent routine blood tests and a general medical examination. This was followed by a 2-week run-in period, during which time no medication was provided for any patients, including those who were receiving, or who had recently received, anti-depressant or psychotropic drugs. After this time, patients were randomly distributed amongst one of three groups, group A receiving two tablets once daily of SHR-5 standardized extract (340 mg/day), group B receiving two tablets twice daily of SHR-5 standardized extract (680 mg/day), and group C receiving two placebo tablets once daily. The distribution of subjects within groups was carried out, according to the principles of total randomization, whereby each patient was randomly assigned an integer 1–90.

The number selected provided the identification code for the patient and the drug code number (randomly encoded in a drug list), and both were recorded in a protocol and in the journal for each patient in order to permit subsequent identification. Information concerning the content of extracts became available to the investigators and volunteers only after completion of the study and final statistical analysis of the results.

A sample size of 30 subjects per group was estimated to be sufficient for a 1–5% significance level by assuming a 30% effect difference between the treatment groups and the placebo group over the study period, with a 95% confidence interval. A total of 91 patients, 31 in group A and 30 each in groups B and C, formed the initial baseline set.

BDI and HAMD questionnaires were administered to subjects at the start (day 0) and the end (day 42) of the 6-week period of treatment. Throughout the study phase, patients were followed-up by telephone contact or personally by attending physicians, and any adverse events were recorded. At the end of the study, patients underwent further routine blood tests and a general medical examination. All complaints arising from the use of the study medications were documented by the

attending principal investigator, physicians and monitors in order to assess the safety of the materials employed. Compliance with the regime of medication by individuals was determined by collecting the used jars and unused tablets on the last visit, and by questioning of the patients by the investigator. Deviations from required protocols were recorded together with the reason and the date.

All data, including signed written consents, personal information, clinical reports, medical histories, results of BDI and HAMD assessments, adverse reaction reports and reasons for study termination, were collected in a journal for each patient, which was signed by the principal investigator and the study monitor.

Parameters for measuring efficacy of treatment

The efficacy of medication with respect to depressive symptoms was assessed from the symptom scores in the BDI and HAMD questionnaires administered at the start and at the end of the treatment period. The primary efficacy variable was represented by the change in total BDI and HAMD scores over the study period. Secondary efficacy variables were classified as the changes, over the study period, in the HAMD symptom indicator subgroups I (points 4, 5 and 6: insomnia), II (points 9 and 10: emotional instability), III (points 12–16: somatization and hypochondria) and IV (points 17 and 18: self-esteem), which reflect the different somatic and physiological aspects of mild and moderate depression.

Statistical methods

The data for each subject, identified only by the entry number of the patient, were entered into the study database. Data management and statistical analyses were performed using PRISM Statistical Software (version 2.01, 1996). The statistical analyses were performed according to Student's *t*-test and the Wilcoxon nonparametric two-tailed rank test. Pearson's correlation was used to test for correlation between variables. The study was planned with adaptive interim analyses (14) following treatments involving three groups of 30 patients. The overall type 1 error rate was set at $\alpha = 0.05$, implying a nominal level of $\alpha = 0.0299$ for the assessment of the statistical significance in the interim analyses.

It was estimated that a sample size of 30 patients per group would permit detection of a standardized treatment difference of 0.50 with a power of 80% (two-sample *t*-test: $\alpha = 0.05$: one-sided).

Results

A total of 91 patients, with mild to moderate depression, were initially selected according to the inclusion and exclusion criteria, and 89 were randomized to one of three treatment groups, treatment group A and B and a placebo group C. Two patients dropped out of the study for non-medical reasons. No patients reported serious adverse side-effects of the medications and none were excluded through non-compliance with the prescribed treatment. The distribution by sex and the mean ages of the 89 participants who completed the study are presented in Table 1. No statistically significant differences in demographic data could be determined between the groups.

Tables 2 and 3 show the HAMD scores at the start of the study (day 0) and following treatment (day 42), which involved the administration of tablets containing either SHR-5 standardized extract (340 mg/day—group A; 680 mg/day—group B) or placebo (group C). There were no statistically significant differences (n.s.) in the mean HAMD and BDI scores between the three groups prior to the start of the treatment. However, the scores obtained by subjects in groups A and B after 42 days of treatment with SHR-5 indicated the presence of significantly ($P < 0.0001$) reduced total levels of symptoms (Fig. 1). Thus, in groups A and B, the mean total HAMD scores declined from 24.52 to 15.97 ($P < 0.0001$), and from 23.79 to 16.72 ($P < 0.0001$), respectively, whilst the score of the placebo group C showed no such improvement (mean HAMD score of 24.17 before treatment vs. 23.41 after treatment ($P = 0.3306$). The mean total HAMD scores for groups A and B at the end of the study were statistically significantly different ($P < 0.001$) from that of group C (Tables 2 and 3).

Fig. 2 shows the efficacy of the SHR-5 standardized extract, as administered to subjects suffering from mild to moderate depression, with respect to changes in insomnia, emotional instability and the level of somatization (Fig. 2a–c, respectively), whilst the intensity of these symptoms of depression, as determined from the scores in the HAMD symptom indicator subgroups, were similar in the treatment groups A and B and the placebo group C prior to the start of treatment. Statistical significant improvements were shown in the subjects of both treatment groups, but not of the placebo group.

In contrast, the initially low levels of self-esteem determined in subjects of all groups at the start of the study (Fig. 2d), remained unchanged after 42 days of treatment with two tablets daily of SHR-5 (group A) or with placebo (group C), but improved significantly (2.690

Table 1. Characteristics of selected patients suffering from mild and moderate depression randomized into treatment groups within the study.

Group	Males	Females	Age (years), mean $\pm s$
Group A (verum) ($n = 31$)	10 (32.3%)	21 (67.7%)	44.9 ± 11.5
Group B (verum) ($n = 29$)	12 (41.4%)	17 (58.6%)	44.60 ± 25.49
Group C (placebo) ($n = 29$)	14 (48.3%)	15 (51.7%)	42.80 ± 12.87

s, standard deviation.

Table 2. Total scores obtained by patients suffering from mild and moderate depression in treatment groups A and B (verum) and the placebo group C submitted to Hamilton Rating Scale for Depression (HAMD) questionnaires before (day 0) and after (day 42) treatment.

	Group A (verum), two tablets SHR-5/day		Group B (verum), four tablets SHR-5/day		Group C (placebo)	
Day of treatment period	0	42	0	42	0	42
Number of patients questioned	31	31	29	29	29	29
Mean HAMD score	24.52	15.97	23.79	16.72	24.17	23.41
s	2.249	4.637	1.698	4.174	1.692	3.803
SE	0.4039	0.8328	0.3154	0.7751	0.3142	0.7063
95% confidence interval						
Lower limit	23.69	14.27	23.15	15.14	23.53	21.97
Upper limit	25.34	17.67	24.44	24.44	24.82	24.86
Coefficient of variation	9.17%	29.04%	7.14%	24.96%	7.00%	16.24%
Within group comparison of mean HAMD scores before (day 0) and after (day 42) treatment						
Comparison within group	A		B		C	
P-value (paired *t*-test)	<0.0001		<0.0001		0.33	
Difference between mean scores	Highly significant		Highly significant		Not significant	
Therapeutic effect demonstrated	Yes		Yes		No	
Between group comparison of mean HAMD scores before treatment (day 0)						
Comparison between groups	A and B		A and C		B and C	
P-value (paired *t*-test)	0.077		0.51		0.19	
Difference between mean scores	Not significant		Not significant		Not significant	
Between group comparison of mean HAMD scores after treatment (day 42)						
Comparison between groups	A and B		A and C		B and C	
P-value (paired *t*-test)	0.34		*P* <0.0001		*P* <0.0001	
Difference between mean scores	Not significant		Highly significant		Highly significant	

s, standard deviation.

before treatment and 1.897 after treatment, $P = 0.0002$) after medication with four tablets daily of SHR-5 (group B).

Discussion

Previous research concerning the pharmacological effects of *R. rosea* extract has focused mainly on its ability to increase mental performance under stress and to relieve temporary fatigue. During the last decade or so, *R. rosea* has been used extensively as a herbal remedy for negative stress reactions, and the number of physicians prescribing the drug, especially in northern Europe, has increased. Our own clinical experience, combined with experience from colleagues using

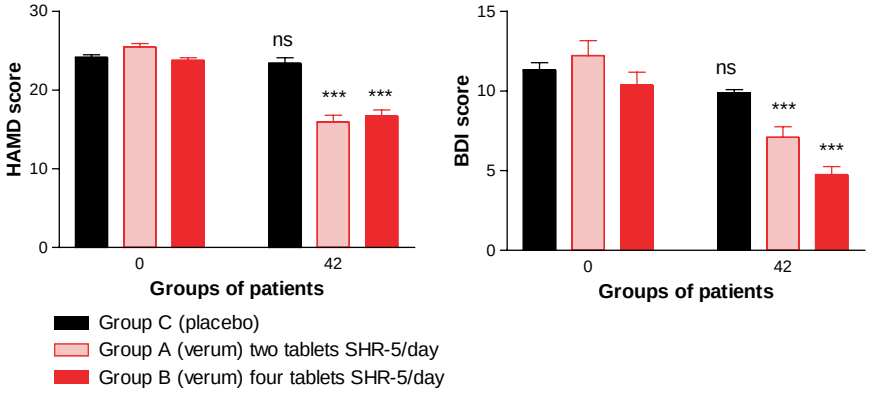

Fig. 1. The effect of treatment with SHR-5 (groups A and B) vs. placebo (group C) as measured by the primary efficacy variable, namely, the change in total Hamilton Rating Scale for Depression (HAMD) and Beck Depression Inventory (BDI) scores between the start (day 0) and the end (day 42) of medication. (For the within-group comparisons of mean scores at days 0 and 42 the significance of the differences are shown as: ns, not significant, and ***, significantly different with $P < 0.0001$).

Table 3. Total scores obtained by patients suffering from mild and moderate depression in treatment groups A and B (verum) and the placebo group C submitted to the Beck Depression Inventory (BDI) questionnaire prior to (day 0) and after (day 42) treatment.

	Group A (verum), two tablets SHR-5/day		Group B (verum), four tablets SHR-5/day		Group C (placebo)	
Day of treatment period	0	42	0	42	0	42
Number of patients questioned	31	31	29	29	29	29
Mean HAMD score	12.23	7.097	10.38	4.750	11.33	9.897
s	5.214	3.636	4.296	2.744	2.440	5.659
SE	0.9364	0.6531	0.7978	0.5185	0.4455	1.051
95% confidence interval						
Lower limit	10.31	5.763	8.745	3.686	10.42	7.744
Upper limit	14.14	8.431	12.01	5.814	12.24	12.05
Coefficient of variation	42.64%	51.24%	41.39%	57.76%	21.53%	57.18%
Within group comparison of mean HAMD scores before (day 0) and after (day 42) treatment						
Comparison within group	A		B		C	
P-value (paired *t*-test)	$P < 0.0001$		$P < 0.0001$		0.21	
Difference between mean scores	Highly significant		Highly significant		Not significant	
Therapeutic effect demonstrated	Yes		Yes		No	
Between group comparison of mean HAMD scores before treatment (day 0)						
Comparison between groups	A and B		A and C		B and C	
P-value (paired *t*-test)	0.14		0.40		0.72	
Difference between mean scores	Not significant		Not significant		Not significant	
Between group comparison of mean HAMD scores after treatment (day 42)						
Comparison between groups	A and B		A and C		B and C	
P-value (paired *t*-test)	0.0075		$P < 0.0001$		$P < 0.0001$	
Difference between mean scores	Significant		Highly significant		Highly significant	

s, standard deviation.

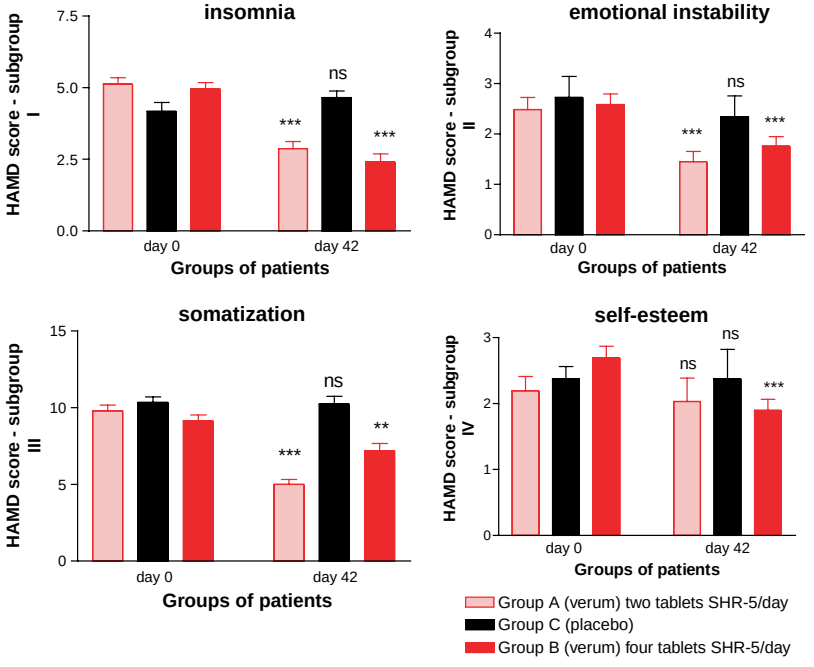

Fig. 2. The effect of treatment with SHR-5 (groups A and B) vs. placebo (group C) as measured by the secondary efficacy variables, namely, the change in the four Hamilton Rating Scale for Depression (HAMD) subgroups: (a) insomnia, (b) emotional instability, (c) somatization and (d) self-esteem (corresponding to the different somatic and physiological aspects of mild and moderate depression) between the start (day 0) and the end (day 42) of medication. (For the within-group comparisons of mean scores at days 0 and 42 the significance of the differences are shown as: ns, not significant, **, significantly different at $P < 0.001$, and ***, significantly different with $P < 0.0001$).

R. rosea as a treatment, is that the positive effect of the drug is mediated by mood stabilization and energy restoration. This is the first randomized controlled study that confirms the potential anti-depressive effects of *R. rosea* as mono-therapy.

The present clinical study has shown that the standardized extract SHR-5 from *R. rosea* possesses a clear and significant anti-depressive activity in patients suffering from mild to moderate depression. When administered in a dosage of two tablets, each containing 170 mg of extract, daily over a 6-week period, statistical significant reduction in the overall symptom level of depression as well as in specific symptoms of depression, such as insomnia, emotional instability and somatization, could be demonstrated. In higher doses, four tablets per day over a 6-week period, an additional positive effect could be shown, the level of self-esteem increased significantly. No side-effects resulting from treatment with SHR-5 could be detected in any group of the groups.

Future studies with follow up period up to 12 weeks as well larger multicenter studies, could eventually answer the question of how SHR-5 compares with the classic anti-depressants in efficacy.

Such studies could also focus on of the pharmacological mechanisms for the mode of action for *R. rosea* in mild to moderate depression.

Acknowledgements—This study was funded with project grants from the Swedish Herbal Institute. The funding sponsor, however, had no role in any practical aspect of the study including collection, management, analysis and interpretation of the data, or review and approval of the manuscript. The study was conceived by AP, the protocol was formulated by VD, and the ethical application was administered by GA. VD enrolled patients and performed the study interventions, the assays and, together with EA, the data analysis. CM drafted the manuscript, and all authors were involved in its critical appraisal and final approval. The authors wish to thank the volunteers for their invaluable help with the study. (The use of SHR-5 for the treatment of depression is the subject of pending patent application by Swedish Herbal Institute.)

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