

A Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Standardised Extract SHR-5 of the Roots of *Rhodiola rosea* in the Treatment of Subjects with Stress-Related Fatigue

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Key words

- *Rhodiola rosea* L.
- Crassulaceae
- stress
- fatigue
- clinical trial

Abstract

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The aim of the study was to assess the efficacy of the standardised extract SHR-5 of roots of *Rhodiola rosea* L. in the treatment of individuals suffering from stress-related fatigue. The phase III clinical trial took the form of a randomised, double-blind, placebo-controlled study with parallel groups. Participants, males and females aged between 20 and 55 years, were selected according to the Swedish National Board of Health and Welfare diagnostic criteria for fatigue syndrome. A total of 60 individuals were randomised into two groups, one ($n=30$) of which received four tablets daily of SHR-5 extract (576 mg extract/day), while a second ($n=30$) received four placebo tablets daily. The effects of the extract with respect to quality of life (SF-36 questionnaire), symptoms of fatigue (Pines' burnout scale), depression (Montgomery-Asberg depression rating scale – MADRS), attention (Conners' computerised continuous performance test II – CCPT II), and saliva cortisol response to awakening were assessed on day 1 and after 28 days of medication. Data were analysed by between-within analyses of variance. No serious side effects that could be attributed to the extract were reported. Significant post-treatment improvements were observed for both groups (placebo

effect) in Pines' burnout scale, mental health (SF-36), and MADRS and in several CCPT II indices of attention, namely, omissions, commissions, and Hit RT SE. When the two groups were compared, however, significant effects of the SHR-5 extract in comparison with the placebo were observed in Pines' burnout scale and the CCPT II indices omissions, Hit RT SE, and variability. Pre- versus post-treatment cortisol responses to awakening stress were significantly different in the treatment group compared with the control group. It is concluded that repeated administration of *R. rosea* extract SHR-5 exerts an anti-fatigue effect that increases mental performance, particularly the ability to concentrate, and decreases cortisol response to awakening stress in burnout patients with fatigue syndrome.

Abbreviations

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CCCPT II: Conners' computerised continuous performance test II
HPA: hypothalamic-pituitary-adrenal
ICD: International Classification of Diseases
MADRS: Montgomery-Asberg depression rating scale
QoL: quality of life

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Bibliography

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Introduction

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Stress-related fatigue is a widespread problem in the Western world. Psychological stress, for example, can often induce long-term exhaustion and diminished interest, producing a condition known as burnout syndrome. This disorder is characterised by a state of continuous physical weakness, a mood of depression, lack of drive, poor concentration, difficulty in sleeping, tiredness, and listlessness [1]. In cases where efficient

and affordable treatment for the syndrome is unavailable, plants that have been traditionally used as stimulants may offer potential application.

In this context, *Rhodiola rosea* L., also known as “roseroot” or “golden root,” has a long history as a valuable medicinal plant and has appeared in the *Materia Medica* of a number of European countries [2], [3]. In the early 19th century, for example, preparations of *R. rosea* were already being used in France as a “brain tonic” [4]. More-

over, roots and rhizomes of *R. rosea* have been employed in traditional folk medicine to increase physical endurance, work performance, longevity, and resistance to high-altitude sickness and to treat fatigue, anaemia, cancer, impotence, and nervous system disorders [6]. In more recent times, extensive studies of the stimulant and stress-protective (or adaptogenic) properties of extracts of *R. rosea* were conducted in the USSR [5], [6], [7], [8], [9], [10], and preparations of the drug now form part of the official medicine of Russia and other members of the former USSR [11], [12], [13]. In Sweden, *R. rosea* was recognised as an adaptogen and a botanical medicine in 1985, and it is classified in the Swedish Drug and Therapy handbook (Läkemedelsboken 1997/98) as one of the most commonly used psychostimulants in the group of officially registered herbal medicinal products [14]. The plant has also been described as possessing stimulant and general strengthening properties. The registered preparations Rosenrot and Arctic Root, which are based on the proprietary extract SHR-5 of *R. rosea*, are extensively used in Sweden and other Scandinavian countries to increase attention and endurance in cases of decreased performance such as fatigue and sensation of weakness.

The stimulant effect of *R. rosea* regulates brain function, decreases fatigue and stress- and corticotropin-releasing factor-induced anorexia in rats [15], and increases working capacity, tolerance to anoxia, and resistance to microwave irradiation and poisoning by toxins [5], [7]. Moreover, *R. rosea* has been reported to improve the learning behaviour of rats and to induce significant improvements in long-term memory [16]. These findings were recently confirmed in experiments on rodents in which an extract of *R. rosea* induced significant adaptogenic, stimulating, and antidepressant- and anxiolytic-like effects [17], [18]. In addition, *R. rosea* may enhance emotional tone by influencing biogenic monoamine neurotransmission in regions of the brain involved in mood and stress regulation, such as the amygdala, hippocampus, hypothalamus, and midbrain. The direct stimulation of nicotinic, cholinergic, noradrenergic, 5-hydroxytryptaminic, and dopamine receptors in selected brain regions may contribute to the adaptogenic effects of *R. rosea* [7], [16]. In studies involving human subjects, *R. rosea* and an active principle rhodiolide (salidroside) have been shown to improve mental performance and the ability to concentrate [6], [10], [19], [20], [21]. Additionally, several investigators have suggested that *R. rosea* may help individuals with mental and physical fatigue resulting from stress conditions [19], [20], [21].

The objective of the present study was to determine whether the daily intake of *R. rosea* extract SHR-5 over a 28-day period would produce any positive effects on attention, quality of life, and symptoms of fatigue and depression in subjects with stress-related fatigue. Salivary cortisol levels were used to assess the anti-stress and anti-fatigue effect of the medication, as it has been shown that patients with chronic fatigue syndrome present a higher cortisol response to the mild stressor of morning awakening [22].

Materials and Methods

Details of the project were submitted to and approved by the Swedish Medical Product Agency (Läkemedelsverket, Uppsala, Sweden) and the ethical committee of the University of Uppsala. The study was conducted in compliance with the revised Declaration of Helsinki [23].

Study population

The study population included subjects of both sexes within the age range 20–55 years who were experiencing difficulties equivalent to the criteria of “fatigue syndrome” according to subdivision F43.8A of the International Classification of Diseases (ICD) code F43.8 “Other reactions to severe stress” [24] as suggested by the Swedish National Board of Health and Welfare [1]. In order to fulfil these criteria, subjects must exhibit daily symptoms of fatigue, enduring for at least 2 weeks, related to a specific stressor that has been present for at least 6 months, and their daily functioning must be significantly negatively affected. Such symptoms must not be related to substance abuse or psychiatric or other primary disorders. The diagnosis of “fatigue syndrome” differs from that of “chronic fatigue syndrome” with regard to a number of points. For example, the former requires the identification of specific stressors whilst the latter focuses on the immune system and symptoms of pain in the lymph nodes, joints, and muscles.

An advertisement describing the purpose of the study and containing a brief outline of the inclusion and exclusion criteria was published, and potential participants responded with subjective ratings and answers to questions covering the selection criteria. All written material, including the ratings of the Pines' burnout scale [25] and a somatic symptom evaluation, together with additional questions concerning time and causes, was taken into account by the licensed physician who made the diagnosis. Pregnant or lactating subjects; individuals presenting comorbidity of other serious diagnoses (e.g., heart disease, stroke, insulin-dependent diabetes, or cancer); those with stomach ulcers, food or medication allergies, asthma, psychosis, or depressive episodes; and those addicted to drugs or who consumed high levels of alcohol or nicotine were excluded.

Volunteers were provided with complete information about the project and an informed consent form to sign before commencing the study. Subjects were recruited and tested in stress rehabilitation clinics belonging to the same organisation and located in three towns in Sweden (i.e., Stockholm and two smaller towns to the north of Stockholm). The same test leader conducted the tests in all three locations using the same equipment in similar rooms normally used for psychotherapy. Subjects were comfortably seated in an armchair during the test period.

Study medications

All test materials were manufactured according to Good Manufacturing Practice by the Swedish Herbal Institute (Gothenburg, Sweden) and presented in the form of sugar-coated white tablets. The verum tablets (390 mg; batch number 8451309) each contained 144 mg of proprietary *Rhodiola* extract SHR-5 (drug extract ratio 4:1; extraction solvent 70% ethanol). The amounts of the active ingredients rhodiolide (4.0 mg/tablet), rosavin, tyrosol, and triandrin were determined by analytical RP-HPLC using an acetonitrile-water gradient system as mobile phase. Peaks were detected by UV-PAD and analytes were quantified at 221 nm (rhodiolide and tyrosol), 252 nm (rosavin), and 262 nm (triandrin). Analytical methods were validated for selectivity, peak purity, precision (RSD < 5%), and accuracy in the range 50–150% of the target amounts of analytes in the tablets in accordance with ICH guidelines [26] using Effi Validation 3 software (version 1.03) for testing and calibration laboratories subject to EN ISO/IEC 17 025:2001 [27]. Placebo tablets (390 mg) were prepared using inactive ingredients that were identical to verum tablets together with 191 mg of dicalcium

phosphate. Medications were packed in plastic jars containing 120 tablets of either verum or placebo tablets (all tablets being identical in appearance and organoleptic properties), and these were subsequently randomised at the factory and marked with random numbers in a random order. Each medication pack bore a code number (encoded in a drug list that was kept by the sponsor and not opened until after all data had been collected) on a label that was designed in accordance with guidelines for Good Clinical Practice, together with a small supplementary label with information concerning the dosage regime.

Procedure

On day 1 of the study the participants met with the test leader, completed the subjective pre-treatment evaluations, and underwent Conners' computerised continuous performance test II (CPT II) [28]. Participants were supplied with an individual medication pack (picked at random by the test leader, who had no knowledge of whether it contained placebo or verum tablets), a supply of Salivette cotton rolls (Sarstedt) for the collection of saliva, and a set of instructions. Individuals were required to collect samples of saliva (see below) at specific times after awakening each day (starting from day 2) and were instructed to take four of the tablets provided daily, specifically, two in the morning and two at lunchtime, starting from day 2 for a period of 28 days. After this time, the subjects met with the test leader, returned the unused tablets together with the original container, completed the post-treatment subjective evaluations, and underwent a CPT II. Compliance with the medication regime was determined from the number of unused tablets returned.

Test methods

The primary endpoint was a reduction in fatigue symptoms assessed according to the Pines' burnout scale [25], a questionnaire with good psychometric properties. The Swedish translation has been used often and is well tested [29]. The reduction in depressive symptoms was estimated using the Montgomery-Asberg depression rating scale (MADRS) [30], a subjective measure of depressive symptoms that are sensitive to change, for which good psychometric properties have been reported. Quality of life (QoL) was measured using the SF-36 questionnaire, which represents the most commonly used instrument for estimating QoL and presents good psychometric properties [31], [32], [33]. The more general indices of physical health and mental health were employed in the present study.

Cortisol response to awakening was determined from saliva samples according to the principle employed in various studies of burnout syndrome and chronic fatigue syndrome [22], [34], [35]. Saliva sampling was chosen because it is a simple, non-invasive, non-stressful method that participants can carry out in their own homes, and the samples accurately reflect the levels of the free fraction of cortisol in plasma. Saliva samples were collected using Salivette cotton rolls, which participants were instructed to place in the mouth for at least 1 min or until the cotton roll was soaking wet. Participants were asked to take the first sample directly upon awakening while still in bed and again at 15, 30, and 60 min after awakening. The samples were maintained frozen (-18°C) until analysed. Levels of cortisol in saliva were measured using Spectria [^{125}I]-Coated Tube Radioimmunoassay kits (Orion Diagnostica). The within-assay coefficients of variation have been reported to range from 0.5 to 6, whilst those between assays never exceeded 10% [22]. The area under the response curve was used as an index of response. The response

curve is typically higher in fatigued subjects and indicates hypothalamic-pituitary-adrenal (HPA) axis functioning.

Attention was assessed using the CCPT II [28]. This method has been used previously to evaluate treatments, and there is evidence that it is sensitive to changes [36]. The five most important indices retrieved from the test were omissions (not responding when a response is required), commissions (responding when a response is not required), response reaction time (Hit RT), the standard error of the reaction time (Hit RT SE), and variability of the response, all of which measure different aspects of attention. Attention and memory deficiency are common in a fatigued population, whilst attention span and information-processing speed are typically lowered in patients presenting chronic fatigue, although the causes of this are unclear [37].

Statistical analyses

The results of the subjective measures and the performance tests were analysed using two-way, between-within analyses of variance (ANOVA), in which an interaction effect indicates a different response over time between the two groups and would, therefore, signal a treatment effect. A significant main effect on a group in the absence of any significant interaction effects would be interpreted as a randomisation failure. A significant main effect of time in the absence of a significant interaction effect would indicate a change over time in both groups and could thus be interpreted as a placebo effect or a general effect of taking the tests and ratings twice and/or a regression towards the mean.

The levels of cortisol in saliva were evaluated by three-way ANOVA in which main and interaction effects of group (treatment \times control), time (pre-treatment \times post-treatment), and response (0, 15, 30, and 60 min after awakening) were analysed. Any interaction effect with time and group would suggest a treatment effect. Cortisol values were logarithmised prior to analysis owing to the excessive skewness of the distribution.

All statistical analyses were carried out using STATISTICA 8.0 software [38] installed on a PC. The alpha level was $P < 0.05$, and the level for tendency was $P < 0.10$. No corrections were made for mass significance.

Results



A total of 60 individuals matching the inclusion criteria, but not the exclusion criteria, were recruited for the study. Using a straightforward double-blind randomisation procedure without stratifications or blocks, 30 individuals received medication with *R. rosea* and 30 received the placebo. As shown in **Table 1**, the treatment and placebo groups included exactly the same proportion of men (10%) and women (90%), while the differences between the two groups in terms of mean age and number of subjects taking psychotropic medication were very small and not statistically significant. Moreover, the percentage of the study period that subjects spent on sick leave was identical in each group. In contrast, there was a noticeable (but not significant) difference in the level of compliance with the medication regime between the two groups, in that the number of tablets missed by those receiving *R. rosea* was greater than that of the placebo group. The distribution (SD) of compliance differed to some extent between the two groups, with the number of tablets remaining in the container ranging from 0 to 75 in the treatment

Table 1 Characteristics of the treatment and placebo groups at the start of the study and level of compliance with the medication regime during the study period.

	Treatment group (n = 30)	Placebo group (n = 30)	t/ χ^2	P
Number of women	27 (90%)	27 (90%)	0.00	1.00
Age ^a	41.0 (7.9)	42.1 (8.5)	0.52	0.60
On sick leave (average percentage)	33.3 (42.7)	33.3 (41.7)	0.00	1.00
Number on psychotropic drugs	7 (23%)	9 (30%)	0.34	0.56
Compliance (number of tablets left) ^a	18.8 (19.8) ^b	11.7 (6.0) ^b	1.82	0.07

^a Values shown are means (standard deviations).

^b For the treatment group $n = 29$; for the placebo group $n = 28$.

group (four subjects omitted to take 45 tablets or more), and from 2 to 29 in the placebo group. Three tablet containers (one in the treatment group and two in the placebo group) were not returned at the end of the study period (● **Table 1**). No adverse events occurred during the period of study, and no major side effects that could be clearly linked to the study medication were reported by any of the subjects.

Missing data

One subject recruited to the treatment group did not show up after the pre-treatment measurements, despite reminders by telephone, e-mail, and letter, and was excluded from all further analysis. The results of the post-study CPT II test were lost for one subject in the treatment group owing to an unidentified computer problem. Three subjects in the placebo group presented results in the post-study CPT II test that indicated an invalid protocol [28]. According to the manual associated with this test, this outcome could have resulted from a misunderstanding of the instructions, a lack of motivation, distraction during the test, an (unidentified) technical problem, or serious neurological impairment (although this cause was considered unlikely, as it had not been indicated elsewhere). The results of the post-study CPT II test gained by these subjects were not used in the analysis of test performance.

The collection of saliva for the determination of cortisol levels was problematic for a number of subjects. Some of the test Salivettes were “dry” on arrival at the laboratory, probably because subjects did not keep the cotton rolls in their mouths for a sufficient length of time. Others subjects failed to send samples to the laboratory as instructed. For these reasons, at least one of the saliva samples was lost for eight subjects in the treatment group (8/29) and for five in the placebo group (5/30).

Subjective measures of quality of life, symptoms, and functioning

The subjective data obtained from Pines' burnout scale, the general indices physical health and mental health of the QoL SF-36 questionnaire, and the MADRS are presented in ● **Table 2**. A statistically significant interaction effect between time and group was detected in the Pines' burnout scale, indicating that the treatment group had benefited more than the placebo group. A tendency ($P < 0.1$) towards a positive effect of treatment on physical health was also noted. The significant main effects of time with respect to Pines' burnout scale, mental health, and MADRS all showed a positive change over time for both groups, and this can be interpreted as a general placebo effect or a general effect of taking the tests and ratings twice and/or a regression towards the mean. No main effects were found for group differences (see ● **Table 2**).

Effects on attention

Significant interaction effects between time and group were detected with respect to omissions, Hit RT SE, and variability indices derived from the CPT II, all of which indicated a more positive change in the treatment group than in the placebo group (● **Table 3**). A tendency ($P < 0.1$) towards a positive effect of treatment on Hit RT was also noted. The significant main effects of time with respect to omissions, commissions, and Hit RT SE showed a positive change over time for both groups. No main effects were found for group differences (see ● **Table 3**).

Levels of cortisol in the saliva

A three-way ANOVA with group (treatment × control), time (pre-treatment × post-treatment), and response (0, 15, 30, and 60 min after awakening) as independent variables was performed. The analysis showed, as expected, a significant main effect of re-

Table 2 Results (mean and SD) of the subjective measurements of quality of life, symptoms, and functioning for the treatment and placebo groups, showing interaction effects between time (2 levels) and group (2 levels)

	Treatment group (n = 29)				Placebo group (n = 30)				F _{time*group} (1.57)	P
	Pre-treatment		Post-treatment		Pre-treatment		Post-treatment			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Pines' burnout scale	4.27	0.54	4.01	0.58	4.33	0.56	4.26	0.51	4.13*	0.047
Physical health (SF-36)	40.94	12.56	43.63	11.74	45.58	10.65	44.83	11.44	3.80	0.056
Mental health (SF-36)	27.30	11.24	32.79	12.28	23.10	9.43	30.99	9.14	0.97*	0.33
MADRS	19.17	7.66	15.66	7.93	21.72	6.58	17.40	8.28	0.22*	0.64

* Significant main effect of time ($P < 0.05$).

Table 3 Results (mean and SD) of CCPT II for the treatment and placebo groups, showing interaction effects between time (2 levels) and group (2 levels).

	Treatment group (n = 28)				Placebo group (n = 27)				F _{time*group} (1.53)	P
	Pre-treatment		Post-treatment		Pre-treatment		Post-treatment			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Omissions	6.29	4.68	2.41	3.24	4.70	4.12	4.29	3.57	5.62*	0.02
Commissions	16.48	7.47	11.19	6.15	16.93	7.37	12.86	7.64	0.89*	0.35
Hit RT	357.00	46.44	354.61	42.45	354.43	50.03	365.54	49.95	3.67	0.06
Hit RT SE	5.83	1.91	4.87	1.30	5.22	1.05	5.44	1.71	12.33*	0.001
Variability	9.36	5.58	6.24	3.16	7.14	2.54	7.97	4.57	8.53	0.005

* Significant main effect of time ($P < 0.05$).

response, representing the presence of an overall saliva cortisol response, a finding that has been well documented in earlier studies [22], [34]. Even without taking group membership into account, an interaction effect could be detected in the study population between time and response, indicating that the pre-treatment response pattern differed from that observed post-treatment. When group membership was considered, a significant interaction effect between group, time, and response was noted, signifying differential pre-treatment and post-treatment response patterns between the two groups (see **Table 4**). As can be observed in **Fig. 1**, the response curve displayed by the treatment group was lower and flatter after treatment than before treatment in comparison with that of the placebo group. This means that the cortisol response to awakening stress had changed significantly following 28 days of treatment with *R. rosea* extract in comparison with the control group.

Discussion

Various studies have demonstrated the beneficial effect of *R. rosea* extract on the mental performance of human volunteers [6], [8], [19], [20], [21], [39]. The effect of a single dose of *Rhodiola* on the mental performance of 85 healthy subjects was studied by Zotova [39] using Anfimov's letter correction table, which permits the compilation of numerically comparable data characterising the quality and quantity of work performed. The results indicated that, in comparison with placebo, administration of the phytoadaptogen did not affect the number of corrections performed but reduced considerably the number of errors made. In a complementary study, the effect of a single 2.5-mg dose of rhodiolside (an active principle of *R. rosea*) was shown to be highly comparable with that of the plant extract [6]. In a further investigation involving both Anfimov's tables and the

ability to memorise paragraphs of text, 82 volunteers were treated with either *R. rosea* extract or tyrosol (a hydrolysis product of rhodiolside) [40]. It was demonstrated that, whilst neither medication affected the time taken to perform the correction task, both improved the quality of performance, reducing the percentage of errors by 29–35% compared with the control and increasing the volume of the short-term memory as represented by the number of text paragraphs recalled. Using a similar protocol, Komar and co-workers [8] treated 254 healthy subjects with an extract of an adaptogen (either *R. rosea* or *Eleutherococcus senticosus*) or with a tincture of *Mentha* as the control. *Rhodiola* was more active than *Eleutherococcus* in terms of its ability to enhance working capacity (i.e., increase the number of corrected symbols), efficiency/performance (i.e., decrease the number of errors) and speed of information processing and perception. More recently, a randomised, double-blind, placebo-controlled parallel-group clinical study with an extra non-treatment control group was performed in order to measure the effect of a single doses of a standardised extract of *R. rosea* (SHR-5) on the capacity for mental work (psychometric tests) against a background of fatigue and stress [21]. The study, which involved 161 healthy cadets, demonstrated that a dose of either 2 or 3 capsules of the extract (equivalent to 370 or 555 mg of SHR-5 and corresponding to 288 or 432 mg of SHR-5 extract) produced statistically significant anti-fatigue effects in comparison with the placebo.

The anti-fatigue effects of repeated doses of SHR-5 extract have been demonstrated in two double-blind, placebo-controlled clinical trials. Thus, Spasov et al. [20] studied the effect of administration of SHR-5 (one tablet containing 50 mg of SHR-5 taken twice a day) over a 20-day period on healthy students during stressful examinations; they reported that measures of physical fitness, mental fatigue, and psychomotor performance all improved in comparison with the placebo. Moreover, when healthy

	Sum of squares	Degrees of freedom	Mean square	F-value	P
Group	5.93	1	5.93	3.332	0.08
Time	0.75	1	0.75	1.075	0.30
Time × group	0.70	1	0.70	1.006	0.32
Response	8.19	3	2.73	18.537	0.000
Response × group	0.23	3	0.08	0.525	0.67
Time × response	1.07	3	0.36	4.581	0.004
Time × response × group	0.67	3	0.22	2.887	0.038

Note: The independent variables were group (treatment × placebo), time (pre-treatment × post-treatment), and response (0, 15, 30, and 60 min after awakening); the dependent measure was the logarithmised saliva cortisol level.

Table 4 Main and interaction effects indicated by three-way ANOVA.

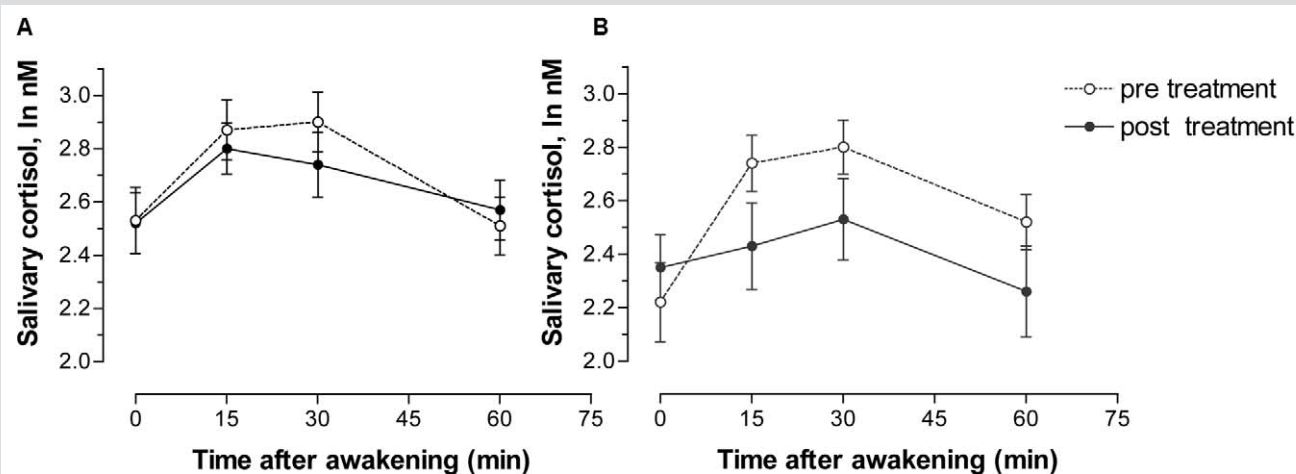


Fig. 1 Cortisol response to awakening in patients with fatigue syndrome showing pre- and post-treatment logarithmised mean values of salivary cortisol with respect to time after awakening for (A) placebo group ($n = 25$) and (B) group treated with *R. rosea* extract SHR-5 ($n = 21$) over a period of 28 days. Vertical bars denote standard deviations.

doctors on night duty received SHR-5 (170 mg of SHR-5 corresponding to 144 mg of SHR-5 extract) for 2 weeks, fatigue scores were reduced and cognitive abilities and total mental performance were increased in comparison with placebo [19].

In the present study, daily administration of 576 mg SHR-5 extract over a 28-day period produced a pronounced beneficial effect in burnout patients, with self-rated fatigue being decreased significantly, with a tendency towards an effect on self-rated physical health. Additionally, a general effect was noted in which both verum and placebo groups showed a positive development over time with respect to several measures. Such an observation could be due to a general placebo effect or a so-called regression towards the mean, which is always a possibility whenever a clinical group is selected.

With respect to performance testing, a significantly greater positive change in the CPT II indices omissions, Hit RT SE, and variability was detected post-treatment in the verum group than in the placebo group. Omissions were less prevalent in both groups after treatment, but significantly more so in the group that had received *R. rosea* extract. The post-treatment standard error of the reaction time was reduced in the treatment group but not in the control group, indicating a more stable work pace, which in turn implies a greater level of attention. Variability, which is also associated with stability of work pace and better attention, was lower in subjects treated with SHR-5 but not in those who had received placebo. A tendency ($P < 0.1$) towards a more positive change in reaction time was noted in the treatment group compared with the placebo group.

Cortisol is a known stress hormone, and it is involved in the feedback regulation of the stress response that helps to restore homeostasis. Subjecting animals and humans to stress produces characteristic changes in the HPA axis, including an increase in the level of cortisol and a reduction in the sensitivity of the HPA to feedback downregulation. Increased levels of serum cortisol have been observed in connection with physical exertion, clinical depression, and various stressors. In chronic stress, prolonged cortisol secretion causes muscle wastage and hyperglycemia and suppresses immune/inflammatory responses [41], [42].

The effect of plant adaptogens in the reduction or prevention of stress-induced damage is characterised by the decrease or total elimination of hormonal changes that are peculiar to stress, such as increased serum cortisol [43], [44]. Free cortisol is present in saliva, and assays of salivary cortisol have been found to be accurate indicators of total plasma cortisol and plasma free cortisol [45]. Furthermore, it is well documented that cortisol levels increase rapidly by around 50–60% after morning awakening and remain elevated for at least 60 min thereafter [46]. Awakening thus acts as a mild stressor, and the measured increase in cortisol caused by such stress provides an indication of the responsiveness of the HPA axis. Patients with burnout have been found to present a relatively high cortisol response to awakening stress [22]. In the present study, the post-treatment cortisol response to awakening stress was significantly different in the group that had received SHR-5 for 28 days than in the control group. These results are in line with our recent demonstration that treatment with *R. rosea* SHR-5 extract for 7 consecutive days prevented the stress-induced increase of cortisol in the blood of rabbits [44]. Generally, the hypersecretion of cortisol is regarded as a marker of a state of depression that remits with clinical improvement [42], [47]. Thus, the inhibition by *Rhodiola* of the cortisol response in stress (i.e., the anti-stress effect) might be associated not only with increased attention and an anti-fatigue effect but also with the recently demonstrated antidepressive effect of SHR-5 in patients suffering from mild to moderate depression [48]. In the present study involving patients with stress-related fatigue, a significant change over time in depressive symptoms was observed in both groups, but with no significant difference between the two groups. It should be noted, however, that fatigue was the primary symptom in the study population selected, and although some individuals exhibited very mild depressive problems, subjects with depression as a major symptom were excluded. Thus, the mean level of depressive symptoms in the population studied was within the range of light depression both before and after treatment for the verum group. If individuals presenting more evident depressive symptoms had been included, or if the study period had been longer, it is possible that different results may have been obtained.

In summary, the results of the present study show that repeated treatment with standardised extract of *R. rosea* (SHR-5) seems to have a positive effect on fatigue level, attention (as measured by a computerised performance test), and saliva cortisol response to awakening stress. Additionally, it is suggested that the inhibitory effect of *Rhodiola* on the increased basal level of cortisol results in an improvement in cognitive function. This proposal is in line with other studies demonstrating that optimal corticosteroid levels are a requirement for efficient cognitive function, as significant changes (up or down) in circulating levels of corticosteroids result in cognitive impairment [49]. The anti-fatigue effects of *Rhodiola* SHR-5 extract, together with improvement in cognitive functions in fatigue and under stressful conditions, were reported earlier in healthy volunteers who had received single and repeated doses of the medication [19], [20], [21]. However, the present investigation constitutes the first demonstration of such effects in patients with chronic stress-induced fatigue. Additionally, this study is the first to demonstrate clinically that *Rhodiola* exerts its beneficial health effects on stress-induced disorders by modulation of the most important stress marker, namely, cortisol. Modulation of cortisol content is considered to be a key mechanism of action of phytoadaptogens [43], [44], and this is fully consistent with the results presented here. It may be concluded that *Rhodiola*, acting as an adaptogen, increases attention and endurance in situations of decreased performance caused by fatigue and sensation of weakness and reduces stress-induced impairments and disorders related to the function of the neuroendocrine and immune systems.

Acknowledgements and Declaration of Interest

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