

Perspective on Roseroot (*Rhodiola rosea*) Studies

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Key words

- *Rhodiola rosea*
- Crassulaceae
- adaptogen
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Abstract

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Rhodiola rosea (roseroot) extract is a commercially successful product, primarily used to reduce the effect of fatigue on physical and mental performance. In this perspective we present our investigation of the most recent studies performed on human subjects. With a focus on the statistical methods we found considerable shortcomings in all but one of the studies that claim significant improvement from roseroot extract. Overall, the study designs have not been well explained. Ex-

perimental results have been confused and appear to be in some cases incorrect. Some of the conclusions are based on selected results and contradicting data have not been adequately taken into account. We point to other studies of higher quality performed on roseroot, several that found no significant effect and one that did. We conclude that the currently available evidence for the claimed effects is insufficient and that the effect of *Rhodiola rosea* is in need of further investigation before therapeutic claims can be made.

Introduction

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Rhodiola rosea (roseroot) is a herbal supplement believed to possess adaptogenic and ergogenic properties and is used primarily to decrease the impact of fatigue on mental and physical performance. Roseroot products are intensely marketed with references to scientific articles. Here we comment on seven studies claiming to have found significant effects [1, 3, 4, 6–9] of treatment of human subjects. Two of the trials [7, 8] were not placebo-controlled, and one [8] was not double-blind or randomized. We focus mainly on the statistical analyses to determine if the conclusions are valid. To our surprise, we have uncovered a number of problems with six of the seven studies [1, 3, 4, 6–8]. The complications include irrelevant comparisons, inappropriate statistical methods, exaggerated conclusions, and several mistakes in the presentation of the data. We are forced to conclude that these trials performed with *Rhodiola rosea* that claim mental and physical enhancements are of poor scientific quality and that their conclusions are not supported by the data.

Reviewed Studies

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Spasov et al. 2000 [1] investigated the stimulating and normalizing effects of *Rhodiola rosea* extract in 40 students aged 17–19 years during a stressful examination period. The physical and mental performance was tested before and after 20 days of *Rhodiola rosea* ingestion. The data have also been published in Russian [2]. The conclusion in [1] was that a significant improvement over placebo had been achieved, but that the dose had been suboptimal.

In this paper [1], Table 1 shows p values for the improvement of verum versus placebo for the functional tests. Table 2 contains descriptive statistics for the placebo and the verum group. A problem was found when we compared the data in Table 2 with the original data in the article in Russian. A majority of the mean values and standard deviations seem to have been rounded off and one differed even more. The control group and the values for the change in heart rate were not included in [1]. The physical work capacity was measured with the standard cycling test PWC-170 and the unit kgm/min. The article in Russian [2] used the same cycling test and the same metric unit, but the values differ greatly. It is difficult to understand why the PWC-170 values

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differ although all other primary data are roughly the same. A remarkable outcome is that the conclusions of the two articles differ even though they are based on the same primary data.

A major complication is found in the conclusion of [1]. The authors base their claim of an adaptogenic effect of *Rhodiola rosea* on a follow-up study that is not described in their article. To our knowledge that study has still not been published.

Darbinyan et al. 2000 [3] described a cross-over trial that tested the effect of *Rhodiola rosea* extract on fatigue during night duty for two randomized groups of physicians. The groups (A and B) with 26 and 30 subjects each received treatment and placebo for two weeks with a wash-out period in-between. The subjects were tested before and after night duty during three periods of two weeks each, with a total of four occasions of night duty. A significant difference was seen in the first period, but not in the last period after the groups had switched treatment. In their conclusions the authors interpreted this as a positive effect for the chosen dose on moderate levels of fatigue. The absence of a significant effect in the last period was claimed to be due to accumulated fatigue in the subjects, caused by the longer period of night duty, meaning that the dose given was not sufficient to give an effect. However, considering that the subjects had only been on night duty for four days during the six-week period of the trial, it seems unlikely that this would cause an accumulation of fatigue. This assumption seems inadequate to explain away the contradictory results of the two groups.

Another study by *Darbinyan et al. 2007* [4] investigated the efficacy and safety of *Rhodiola rosea* treatment in 89 patients with mild to moderate depression. The participants, males and females aged 18–70 years, were randomized into three groups (A, B and a placebo group, C). The trial's results showed significant improvement in the verum groups following the six weeks of medication. The placebo group showed no improvement at all. Under *statistical methods* it is said that three tests were performed: Student's t-test, Wilcoxon rank test and Pearson's test for the correlation between the variables. However, only the results from the t-tests are presented in the article. There is no further mention of the other tests, nor why they were used.

The results from the hypothesis tests are stated in Tables 2 and 3 as p values for three types of comparisons: within the groups (before versus after intake), between the groups *before* the treatment and between the groups *after* the treatment. The authors used the paired t-test in all three cases. This test should only be used for comparing *within* groups. Another error in the test method is that the authors compared the values *before* and *after* treatment separately. Instead, they should have calculated the difference *within* each group and then compared this difference *between* the groups. Hence, the conclusion that the extract from *Rhodiola rosea* possesses a significant antidepressive activity is based on irrelevant tests.

The complete absence of an effect in the placebo group is remarkable. According to Walsh 2002 [5] (a review of 75 placebo-controlled trials on depression) the zero placebo effect in studies of depression is extraordinary. In placebo-controlled trials with patients who have mild to moderate depression, a varied and a substantial placebo effect is often observed. In that survey the response to placebo was never below 10% and could be as high as 50%.

Shevtsov et al. 2003 [6] assessed how a single dose of *Rhodiola rosea* affects the capacity for mental work in a stressful and exhausting environment. Two different doses were tested against a placebo and a control group. The study was carried out on cadets

between 19 and 21 years of age, who performed a series of physical and mental tests before and after treatment. To assess any changes in mental and physical performance, an antifatigue index was calculated by using the difference of the mean scores before and after the intake. The authors found a highly significant improvement for both the lower and higher doses after the intake (41 and 20 subjects, respectively) compared to the control and placebo groups (20 and 40 subjects, respectively).

A nonparametric Mann-Whitney U test was used in the study for testing any difference in fatigue between the four groups. We have recalculated the results from the nonparametric test, using the parametric t-test instead. The results differed more than is likely even if the sample distribution was greatly distorted. The highly significant difference in the article between the placebo and the verum groups, showed no significance in our recalculations. The authors do not comment on the sample distribution in the article which prevents us from drawing any conclusions from these findings.

Table 7 of the paper shows the changes in the pulse pressure, but it does not match the values that are the basis for the results which can be found in Table 2 as systolic and diastolic blood pressure. On recalculation we found an error in the article: the value for the placebo group *before* the intake is said to be 45.3, when it is in fact 47.7 as presented in Table 7. This error creates homogeneous baseline data for all four groups.

The increased pulse pressure for the verum groups was interpreted as proof for increased physical wellness for *Rhodiola rosea* users. This claim is unsubstantiated because pulse pressure increase does not necessarily correlate with improved physical health. It was also the only significantly increased physiological variable.

Fig. 5 shows the Total Anti-Fatigue Index (TAFI) with the mean scores of the functional tests added together as an index for each group. The authors found significant differences in TAFI between placebo and the two verum groups (as shown in Table 4), but not between the placebo and the control group. The values in Table 4 for the verum groups do not match the bars in Fig. 5 due to a mix-up. The verum group with a higher dose has a mean value of 1.0385 in Table 4 but 1.0195 in Fig. 5. This figure is presented with a truncated scale which makes the effect of *Rhodiola rosea* seem much greater than found in the study.

Moreover, there is a considerable number of misprints and mix-ups in this article, and an exceptionally unclear presentation of the data, which indicates that this manuscript was not thoroughly reviewed and edited before publication.

Fintelmann and Gruenwald 2007 [7] compared two doses of *Rhodiola rosea* in combination with vitamins and minerals (Vigodana®), in 120 men and women in the age range 50–89 years with physical and cognitive deficiencies during a period of 12 weeks. The authors found highly significant improvements for all of the tested problems, such as exhaustion, decreased motivation, daytime sleepiness, decreased libido, sleep disturbances and cognitive complaints. Note, however, that no placebo or untreated control group was included in the study.

In the introduction of the article the authors say that many of the symptoms in the elderly, like the ones listed above, are caused by deficiencies of vitamins and minerals, and that the supplementation of these nutrients can cure the symptoms or prevent them from arising. No reference is given to this claim. The authors referred the positive effects of *Rhodiola rosea* to references 3, 9 and 10 evaluated here without noting the problems we describe. Because this study concomitantly gave three treatments with no

control group it cannot be used as evidence for any effect of *Rhodiola rosea*.

Bystritsky et al. 2007 [8] assessed the effect of *Rhodiola rosea* against generalized anxiety disorder (GAD). Ten subjects, nine females and one male, underwent a 10-week open-label treatment phase with *Rhodiola rosea*. The subjects' condition was measured pre- and post-treatment by four different tests (anxiety, depression, etc.). The authors found statistically significant improvements for three of these.

However, this study has several major flaws. There is for instance no placebo control and the sample size is very small. The authors mention these problems under discussion, but still draw the conclusion that *Rhodiola rosea* appears to reduce symptoms of anxiety in individuals suffering from GAD.

Olsson et al. 2008 [9] investigated the antifatigue effect of *Rhodiola rosea* in subjects with burnout suffering from fatigue syndrome. Sixty subjects were randomized into two groups, placebo and treatment. The effects were quantified with tests that measured quality of life, symptoms of fatigue, depression, attention and morning levels of cortisol in saliva. When comparing the groups the authors found statistically significant improvements in favor of the treatment group in three variables: symptoms of fatigue, attention, and cortisol levels.

As far as we can tell, this study appears to be the only one among those that we have investigated that has used a satisfactory experimental protocol and appropriate statistical methods. However, we question the authors' description of the trial as a phase III trial. It would seem more appropriate to call it a phase IIb trial considering the small sample size and multiple endpoints. Also, as in Fintelman and Gruenwald [7], the authors have uncritically cited references 2, 3, 9 and 11 as describing effects of *Rhodiola rosea*.

Discussion

The aim of this investigation is to assess the validity of the most recent or most cited studies performed on *Rhodiola rosea*. All trials evaluated above claimed to have found positive effects of *Rhodiola rosea* extract for various endpoints, but our analysis have lead us to the conclusion that all but one [9] have severe problems that diminish their value. Throughout our work new problems with the studies kept emerging. In this review we have focused on the major problems that we have found – there are many smaller issues that we have had to leave out. Some of the problems are quite extraordinary. For instance, Spasov et al. [1] based their final conclusion on a follow-up study that was not described in their article and remains unpublished. Darbinyan et al. [3] claimed to have found a significant improvement over placebo despite contradictory results that they explained away with an unfounded assumption. The second study by Darbinyan et al. [4] used irrelevant tests and an inappropriate statistical comparison. Bystritsky et al. [8] and Fintelman and Gruenwald [7] claim to have observed an effect but did not use a placebo control. Shevtsov et al. [6] is riddled with misprints and mix-ups which make it difficult for the reader to interpret the text and understand the procedure. Also, the use of pulse pressure as a measure for physical fitness is incorrect, and the levels of statistical significance presented in the study appear unreasonably high.

We have also evaluated studies of *Rhodiola rosea* that found no effects. We approached these studies in the same critical way as the ones mentioned above and deem their results reliable, as we

have not found any major errors. DeBock et al. [10] investigated if acute or chronic ingestion of *Rhodiola rosea* extract had an effect on a variety of exercise, neural and cognitive tests in healthy, young males and females. The trial was divided into two parts. During the first part of the trial the treatment and placebo group performed the tests before and after a single dose of *Rhodiola rosea* extract. After a five-day wash-out period the groups switched treatment and were tested again. During the second part of the trial, the groups were tested before and after receiving treatment for four weeks. In addition to that they received a single dose prior to the testing in exactly the same way as during the first part of the trial. The authors found a positive effect on performance after acute intake of the preparation, but no effect was found after four weeks of treatment. They concluded that an acute dose of *Rhodiola rosea* can modestly affect performance, but that there is no effect to be seen after chronic treatment.

Walker et al. [11] investigated if *Rhodiola rosea* changed the skeletal muscle phosphocreatine recovery in trained men after exhaustive exercise. The study found no influence of *Rhodiola rosea* intake on exercise performance, perceived exhaustion, or muscle phosphate kinetics. Their results supported the studies by Colson et al. [12] and Earnest et al. [13] that also failed to find an impact on performance or any associated physiologic variable, such as heart rate, VO₂ and lactate and ventilation thresholds in cycling exercises. Of the two last-mentioned studies we deem Colson et al. [12] to be less reliable because the trial only included eight subjects.

In another article by Walker et al. [14] the authors reviewed several studies made on *Rhodiola rosea* effects. The general opinion was that trials performed in Eastern Europe tended to show an improving effect of *Rhodiola rosea* on mental and physical attributes, whereas Western European and North American studies only proved an antioxidative effect. They also mentioned that positive studies, such as [3] among others, should be given less weight than the negative one by DeBock et al. [10] because the latter was more clear and interpretable. A review by Roland and Amundstuen [15] concluded that there is insufficient evidence for a potential benefit of medication with *Rhodiola rosea* due to the low number of trials and the fact that they often exhibit weak methodological quality, with a low number of included subjects, insufficient randomization quality and functional testing of mental and physiological variables that are not generally accepted. Our evaluation of the literature leads us to the conclusion that a potential adaptogenic effect of *Rhodiola rosea* is yet to be sufficiently documented in a scientifically satisfying way. It is alarming that poorly conceived and performed studies, such as [1, 3, 4, 6–8], have been published apparently without adequate scientific and editorial scrutiny. They have been cited uncritically by many subsequent studies and are mentioned in numerous advertisements, thereby giving both the scientific community and potential customers a false impression. The Swedish Herbal Institute, a producer of *Rhodiola rosea* extract, has been involved in four of the questioned studies [1, 3, 4, 6].

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