

A Pilot Study of *Rhodiola rosea* (Rhodax[®]) for Generalized Anxiety Disorder (GAD)

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ABSTRACT

Background: *Rhodiola rosea* is an herbal supplement that many in the general population in Russia and elsewhere in the world have used for decades to alleviate everyday anxiety, depression, and insomnia. Whether *R. rosea* is effective in reducing similar symptoms in clinical samples is unknown. The goal of this pilot study was to evaluate whether *R. rosea* is effective in reducing symptoms of generalized anxiety disorder (GAD).

Method: Ten (10) participants with a DSM-IV diagnosis of GAD, recruited from the UCLA Anxiety Disorders Program and between the ages of 34 and 55, were enrolled in this study from November 2005 to May 2006. Participants received a total daily dose of 340 mg of *R. rosea* extract for 10 weeks. Assessments included the Hamilton Anxiety Rating Scale (HARS), the Four-Dimensional Anxiety and Depression Scale, and the Clinical Global Impressions of Severity/Improvement Scale.

Results: Individuals treated with *R. rosea* showed significant decreases in mean HARS scores at endpoint ($t = 3.27$, $p = 0.01$). Adverse events were generally mild or moderate in severity, the most common being dizziness and dry mouth.

Conclusions: Significant improvement in GAD symptoms was found with *R. rosea*, with a reduction in HARS scores similar to that found in clinical trials. These preliminary findings warrant further exploration of treatment with *R. rosea* in clinical samples.

INTRODUCTION

The use of alternative treatments in the United States, specifically herbal remedies, is widespread and increasing at a rapid clip. A recent epidemiologic study found that 42% of a national sample used an alternative therapy in the previous year.¹ This represents an increase from 34% in a similar survey conducted a decade earlier.² Herbal remedies are one of the most common forms of alternative treatments, with estimates of use ranging from 15% to 33% in the general population.^{1,3} In a national study of why patients use alternative medicine, anxiety was found to be one of the strongest predictors (odds ratio 3:1; 95% confidence interval, 1.6–6.0).⁴ Within a 12-month period, 43% of individuals suffering from anxiety report relying on alternative approaches for treatment.¹ Unconventional treatments are often used without advice from either a medical doctor or

licensed alternative practitioner. Given the widespread use of herbal remedies for anxiety, the need for empirical research to verify the efficacy of these treatments is of enormous public and medical interest.

Individuals in Russia, Scandinavia, and Iceland have used *Rhodiola rosea* (also known as Golden Root or Arctic Root) for centuries as a health-enhancing supplement.⁵ Moreover, *R. rosea* preparations have been used extensively since 300 AD in traditional Tibetan medicine for treating lung disease.⁶ *R. rosea* is known as *hongjingtian* in Chinese, (*hong* = red, *jingtian* = view of heaven or heavenly view, probably referring to its growth on high-altitude stone faces) and is in wide use as a traditional Chinese herb.^{7–9} The purported effects of this internationally recognized herb, which is traditionally consumed as a tea, include improved mood, increased sexual potency, enhanced energy, alertness, weight loss, and longevity.⁸ Reports in the United States describe

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R. rosea as a natural alternative to alleviate stress and discomfort.¹⁰ Several Internet postings report “success stories” of *R. rosea* in reducing anxiety and depression.

The physiologic mechanism by which *R. rosea* exerts its effect remain elusive. Russian researchers initially classified *R. rosea* as an adaptogen, that is, a chemical that exerts non-specific effects on the body to permit the normalization of physiologic responses to a variety of stressors.^{35–38} In addition to *R. rosea*, ginseng and Siberian ginseng are other well-known adaptogens from plant sources.

A recent MEDLINE® search resulted in more than 100 articles on *R. rosea*, more than two thirds of which have been published in the last decade.^{11–14} Many of these reports mention reduction in overall stress, fatigue, and irritability—symptoms frequently associated with anxiety disorders, and in particular generalized anxiety disorder (GAD). GAD is a disabling and relatively common condition, with a lifetime prevalence between 5% and 7%.^{15,16} An array of traditional treatment options are available for GAD including benzodiazepines, serotonin reuptake inhibitors, tricyclic antidepressants, and cognitive-behavioral therapy. Nevertheless, over 40% of patients show limited or no response to conventional treatment.¹⁷ In addition, individuals who do respond to established treatment often experience troublesome side-effects that may interfere with their adherence. These factors necessitate the exploration of additional and alternative treatment strategies for GAD that are effective, safe, and tolerable. Herbal remedies may therefore fill this need. Furthermore, since some herbal preparations counteract pharmacologic agents, resulting in unpleasant or life-threatening events, and because of the limited restrictions imposed by the Federal Drug Administration for the marketing of these products, it is imperative to investigate their safety empirically.^{18,19}

R. rosea appears to have an excellent safety profile. Side-effects are relatively uncommon but could include allergy, irritability, insomnia, fatigue, and unpleasant sensations, especially at high doses.⁵ With the use of *R. rosea* expanding and popular culture increasingly recognizing its efficacy and tolerability, scientific investigation of the efficacy of *R. rosea* for treating chronic anxiety disorders is warranted. The objective of this study was to obtain preliminary data on the effectiveness of *R. rosea* for treating GAD. We hypothesized that *R. rosea* treatment would improve GAD symptoms, as reflected in significantly reduced Hamilton Anxiety Rating Scale (HARS) scores at endpoint (week 10 of treatment) as compared to baseline.

METHOD

Study design

This study utilized a 10-week open-label design to evaluate the safety and efficacy of *R. rosea* in the treatment of

GAD. Ten (10) participants were enrolled from November 2005 to May 2006. Participants were recruited from the UCLA Anxiety Disorders Program at the Semel Institute for Neuroscience and Human Behavior, by posting flyers around the UCLA Medical Center, and in a local newspaper. Approval from UCLA’s Institutional Review Board was obtained prior to and throughout the conduct of this study. All eligible participants provided written informed consent prior to the initiation of any study-related procedure.

This study consisted of 3 parts: a screening/baseline visit, a 10-week open-label treatment phase, and a 30-day post-study safety follow-up. Study visits were conducted at baseline and at the end of treatment weeks 3, 6, and 10. Participants meeting all eligibility criteria at baseline were enrolled and received 2 bottles of *R. rosea* and directions to take 1 tablet in the morning and 1 tablet in the evening. Each capsule contained 170 mg of *R. rosea* extract, for a total daily dose of 340 mg. The dose chosen for this study is consistent with dosage information provided by the manufacturer and found in previous clinical reports.^{5,20,21} Each capsule of Rhodax® is standardized to provide 30 mg of each of the following 8 biomers: rosavin, rosarin, salidrosides, rosin, rhodalgin, acetylrhodalgin, rosaridin, and rosaridol. Other ingredients include microcrystalline cellulose, magnesium stearate, and gelatin.^{5,20}

The study medication for this pilot was manufactured for Phoenix Laboratories by Bodyonics Ltd. (Farmingdale, NY) under the brand name Rhodax® (Lot 82529, expiration date October 2008). When the raw materials (containing *R. rosea*) is received at Bodyonics Ltd., it is quarantined for 2 weeks before undergoing microbiologic testing and high pressure liquid chromatography (HPLC). This process ensures accurate identification and potency of raw material in each capsule of Rhodax.

Patient selection

Male or female outpatients aged 18–64 years were eligible if they had a current DSM-IV diagnosis of GAD, confirmed by the Mini International Neuropsychiatric Interview (MINI).²² Participants had to score ≥ 16 on the Hamilton Anxiety Rating Scale (HARS) and < 17 on the 21-item Hamilton Depression Rating Scale (HDRS) at screening to be considered for enrollment.^{23,24} We included participants with lower baseline anxiety scores (i.e., HARS > 16) than typically included in GAD trials (i.e., HARS > 20) to increase external validity of the study. Participants were excluded if they had a primary diagnosis meeting DSM-IV criteria for any other Axis I disorder other than GAD, as were patients who met DSM-IV criteria for mental retardation or any pervasive developmental disorder, or who had any neurologic impairment. Also excluded were those with a current diagnosis or recent history of drug or alcohol dependence, current suicidal ideation and/or history of suicide attempt, or any personality disorder of sufficient severity to interfere with participation in the study. Other exclusion cri-

teria included the presence or history of a medical disease that might place the participant at risk or compromise the integrity of the study. Pregnant or breastfeeding women and women of childbearing potential who were not practicing a reliable form of contraception were also ineligible for the study.

We permitted participants to take stable doses of selective serotonin reuptake inhibitor (SSRI) or serotonin nor-epinephrine reuptake inhibitor medication if they had been taking them for at least 3 months and remained symptomatic. In addition, we permitted participants to take benzodiazepines on an as-needed basis but no more than twice a week. Site personnel contacted all participants 24 hours in advance of their scheduled appointment to remind them of the visit.

Assessments

At screening, GAD diagnosis was confirmed by a psychiatric clinical interview and administration of the Mini International Neuropsychiatric Interview (MINI).²² Psychiatric assessments included the HARS, HDRS, the Clinical Global Impressions Scales for Severity of Illness, and the Clinical Global Impressions of Improvement (CGI-I) (beginning at week 2).^{23–25} In addition, participants completed the Four Dimensional Anxiety and Depression Scale (FDADS).^{25–27} The FDADS is a self-rated, 20-item instrument designed to assess symptoms of anxiety and depression. The FDADS further subdivides anxiety and depression symptoms into 4 dimensions: psychic, physiologic, cognitive, and behavioral. The FDADS demonstrates sound psychometric properties, with good internal consistency and test-retest reliability. Validity has been demonstrated in both clinical and nonclinical samples and by convergence with established measures of anxiety and depression.^{26,27} In this study, the FDADS anxiety subscale was used to subjectively measure symptoms of GAD.

Safety procedures included a physical examination and routine chemistry, hematology, and urinalysis laboratory assessments, both at baseline and endpoint. We also monitored subjective reports of adverse events and participants completed the Side-Effects Checklist at each visit.²⁸

Statistical methods

Data were entered anonymously into a Microsoft Excel spreadsheet and analyzed by the UCLA Semel Institute Statistical Core. The primary efficacy measures were the CGI-I and the HARS. Response to treatment was defined as a reduction of 50% or more on the HARS. Symptom remission was defined as a CGI-I score of 1 or 2 (“very much improved” or “much improved”; respectively) and a score of ≤ 8 on the HARS.

Paired *t*-tests were used to compare mean baseline and endpoint scores on the HARS, the HDRS, and FDADS. All tests were 2-tailed, with a significance level set at $\alpha = 0.05$.

RESULTS

Twelve (12) individuals expressed interest in the study and took part in an initial telephone screen. Seventeen percent (17%) ($n = 2$) of those screened by telephone were deemed ineligible to participate. Reasons for exclusion were psychiatric comorbidity ($n = 1$) and prohibited concomitant medication ($n = 1$). Ten participants enrolled and received *R. rosea* treatment. The mean age of the sample was 44 ± 7.37 years. Of the 10 individuals enrolled in the study, 9 (90%) were female. Three (3; 30%) of the participants took benzodiazepines on an as-needed basis but no more than 2 times per week (alprazolam, $n = 2$; lorazepam, $n = 1$). These participants began benzodiazepine treatment 3 months prior to enrollment and continued throughout the study. One-hundred percent (100%) ($n = 10$) of enrolled participants completed the 10-week treatment phase.

The change from baseline to endpoint in efficacy measures (HARS, HDRS, FDADS, CGI-I) are presented in Table 1. Mean HARS scores at baseline (23.40 ± 6.0) were significantly different than at endpoint (14.10 ± 8.06) ($t = 4.70$, $p = 0.001$). A significant difference was also found between mean baseline (8.50 ± 1.95) and endpoint (5.30 ± 2.54) HDRS scores ($t = 4.70$, $p = 0.001$) and between baseline (68.70 ± 6.7) and endpoint (53.90 ± 7.2) FDADS anxiety subscale scores ($t = 2.35$, $p = 0.043$).

At endpoint, 5 (50%) of 10 participants had at least a 50% decrease on the HARS and were thus considered responders to treatment. Four (4; 40%) achieved a score of 1 or 2 on the CGI-I and an endpoint HARS score of ≤ 8 , meeting criteria for remission. Two (2) additional participants were “minimally improved” on the CGI-I.

Adverse events were mild to moderate, the most common being dizziness ($n = 2$; 20%) and dry mouth ($n = 4$; 40%). No participant discontinued the study prematurely due to adverse events, and no serious adverse events occurred. There were no significant abnormalities in laboratory data after treatment. The 30-day poststudy safety follow-up revealed no subsequent adverse effects.

DISCUSSION

Overall this pilot study suggests that *R. rosea* has anxiolytic effects, as indicated by significant decreases in HARS scores over time. While previous reports have indicated *R. rosea* can provide benefits for several conditions including pain, insomnia, stress, anxiety, and depression, this is the first report of anxiolytic effects in a clinical sample.

The treatment effects in this study results are similar to those found in psychopharmacological trials where the effect size of 1.0 denotes a moderate treatment effect. A meta-analysis of various anxiety disorders treatments found the mean effect size (controlling for methodological variables) for the SSRIs as a group to be 0.82; for clinician behavior

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE STUDY SAMPLE

Participant number	Gender	Age	HARS baseline	HARS endpoint	HDRS baseline	HDRS endpoint	FDADS-anxiety baseline	FDADS-anxiety endpoint	CGI endpoint
1 ^a	M	55	21	10	7	3	70	44	2
2 ^{a,b}	F	54	17	6	6	5	64	42	2
3 ^{a,b}	F	43	27	4	6	3	80	27	1
4 ^{a,b}	F	38	19	20	9	7	59	64	4
5	F	34	24	8	9	3	63	42	2
6	F	41	21	20	12	10	71	78	4
7 ^{a,b}	F	53	24	6	9	2	61	33	2
8	F	40	29	19	10	6	76	64	3
9	F	39	16	22	10	7	48	62	5
10	F	43	36	26	7	7	95	83	3
Mean ± SD		44 ± 7.37	23.40 ± 6.0	14.10 ± 8.06	8.50 ± 1.95	5.30 ± 2.54	68.70 ± 6.7	53.90 ± 7.2	2.8
Paired <i>t</i> -test				<i>t</i> = 3.27		<i>t</i> = 4.71		<i>t</i> = 2.35	
<i>p</i> value				0.01		0.001		0.043	

^aParticipants who met criteria for response.

^bParticipants who met criteria for remission.

HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; FDADS, Four Dimensional Anxiety and Depression Scale; CGI, Clinical Global Impressions.

therapy, 0.99, and for clomipramine, 1.09.²⁹ The effect size in the open pilot study is, to some extent, an artifact of an open trial, where the effect size does not factor out the effect of placebo. Therefore, although this study was not placebo controlled, it demonstrates an effect that is perhaps only slightly better than what one would expect with placebo. Open-label studies with herbal remedies frequently produce high response rates that are not always confirmed in subsequent controlled clinical trials.^{18,19,29–32}

However, the absolute value of the change (9.4 points) compares favorably to that found in several clinical trials (6.01–9.3) and is larger than the average effect of placebo of 7.3 found in meta-analyses of clinical trials with other active medications.^{29,33} This meta-analysis shows a large variability of the effect of placebos depending on the patient population, the exact nature of the treatment program, and baseline patient characteristics. A review of other recent placebo-controlled studies for the treatment of GAD shows similarly a range of effect sizes from $d = 0.74$ to $d = 1.72$, further emphasizing that the effect of placebo treatment is highly dependent on specific characteristics of the study.^{34–36} Thus, comparing our results to the literature does not answer whether we truly found the antianxiety effect of *R. rosea* beyond an expected placebo effect, and emphasizes the necessity for future study.

Another factor that may have influenced placebo-type response is that 3 of the patients in this sample had milder HARS scores (16–20) than for those typically enrolled in GAD trials (usually greater than 20). However, response in this study was independent of baseline scores, and 4 of the 5 responders had baseline HARS scores greater than 20.

On the CGI-I, 2 participants were rated as “no change” and 1 as “minimally worse.” It is not clear why 1 participant had slight worsening of symptoms. Three (3) participants continued taking previous (albeit ineffective) benzodiazepine medication. There was no apparent interaction between *R. rosea* and benzodiazepine use in these participants, suggesting that it may be safe to co-administer both agents. Further research is needed to confirm this.

Although 4 (40%) reported dry mouth and 2 (20%) reported dizziness, the adverse events were mild to moderate and did not result in discontinuation of treatment. *R. rosea*, like other herbal remedies, may appeal to patients who want to avoid the common side-effects of prescription antidepressant and antianxiety medications. Although it was not tested in this study, *R. rosea* has been reported to improve memory, male sexual dysfunction, and help with weight loss.^{37–40} If future studies can verify these benefits, concomitant use of *R. rosea* with SSRIs and SNRIs may prove helpful for these common side-effects.

Interpretation of these results is limited by a small sample size ($N = 10$), use of an open-label design, and fixed dosing schedule. Perhaps the greatest concern in interpreting these data is the extent to which these results represent a placebo response. A placebo-controlled study with enough power to detect significant treatment differences is therefore required to address these concerns more definitively. Despite these limitations, *R. rosea* appears to reduce symptoms of anxiety in individuals suffering from GAD. Given this, a favorable side-effect profile, and the popularity of herbal remedies in our culture, *R. rosea* is deserving of further study in GAD and other stress-related conditions.

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