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The Effects of *Rhodiola rosea* L. Extract on Anxiety, Stress, Cognition and Other Mood Symptoms

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This trial evaluated the impact of a *Rhodiola rosea* L. extract on self-reported anxiety, stress, cognition, and other mood symptoms. Eighty mildly anxious participants were randomized into two different groups of either *Rhodiola rosea* L (2 × 200 mg dose Vitano®, 1 tablet taken before breakfast and 1tablet before lunch) or a control condition (no treatment). Self-report measures and cognitive tests were completed at four testing sessions over a period of 14 days. Relative to the controls, the experimental group demonstrated a significant reduction in self-reported, anxiety, stress, anger, confusion and depression at 14 days and a significant improvements in total mood. No relevant differences in cognitive performance between the groups were observed. *Rhodiola rosea* L (Vitano®) presented a favourable safety tolerability profile. Although this was a non-placebo controlled trial, it is unlikely that the findings were the result of placebo effects as changes appeared gradual and were specific to certain psychological measures. However, we cannot determine a causal relationship; further investigations are recommended to support the effects of *Rhodiola rosea* L. extract on stress related symptoms.

Keywords: Rhodiola rosea L; Stress; Anxiety.

INTRODUCTION

Rhodiola rosea L. (Family Crassulaceae) is a shrub that has been used in traditional medicine to alleviate the symptoms of everyday stressors including anxiety, stress, fatigue and depression (German *et al*., 1999). The pharmacological effects of *Rhodiola rosea* L have been demonstrated in a small number of preclinical (e.g. Chen *et al*., 2009; Mannucci *et al*., 2012; Cayer *et al*., 2013), and clinical studies (Darbinyan *et al*., 2000; Panossian *et al*., 2010; Spasov *et al*., 2000; Darbinyan *et al*., 2007; Sarris, 2007; Bystritsky *et al*., 2008; Sarris *et al*., 2011). For example, Edwards *et al*. (2012) demonstrated that Rosalin—a proprietary dry extract of the *Rhodiola rosea* root—to have significant anti-stress effects after 3 days of treatment. In another study in patients experiencing stress-related fatigue and burnout, male and female participants were given an extract SHR-5 of *Rhodiola rosea L*. for 28 days, with those given the extract showed increased concentration and a decrease in fatigue relative to the controls (Olsson *et al*., 2009). Such findings support the medicinal use of *Rhodiola rosea* in humans.

It is possible that *Rhodiola rosea* L. may have a moderating effect on anxiety and mood by inhibiting physiological stress responsivity. Anxiety, stress and fatigue are widespread in the Western World. In the UK, The Office for National Statistics estimate that 4.7 per cent of adults experience diagnosed generalized anxiety and worldwide; lifetime prevalence of anxiety disorders is 16.6%. This rate is much higher for mild anxiety. The primary aim of this trial was to investigate the effects of *Rhodiola rosea* L on self-reported mild anxiety and stress in a sample of university students. Stress and anxiety are highly prevalent in students, and it is well documented that students are exposed to a range of stressors during their studies (Bewick *et al*., 2010; Alzahem *et al*., 2011; Keyes *et al*., 2012; Zunhammer *et al*., 2013). In the present study, mildly anxious students with scores above 30 on the Spielberger State–Trait Anxiety Inventory (STAI; Spielberger, 1983) were randomly allocated to receive either, a standard dose of *Rhodiola rosea* L. extract (Vitano®) for 14 days, or to a control group without treatment. Our primary outcomes were self-reported anxiety and stress. Secondary outcomes measures included self-ratings of mood, sleepiness and sleep. In addition, we also assessed the effects of *Rhodiola rosea* L. on cognitive function using standardized speed of processing cognitive tasks.

MEASURES AND METHODS

Design. The feasibility study was an open-label, randomized (*Rhodiola rosea* L *vs*. control) repeated measures design. Individuals in the control group did not receive any investigational medicinal product (IMP). The *Rhodiola rosea* L group were given a daily dose of 2 × 200 mg of Vitano® (as recommended in the summary of product characteristics), 1 tablet taken before

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breakfast and one before lunch for 14 days. The active ingredient of Vitano®[1] is Rosalin (WS® 1375), a proprietary dry extract from *Rhodiola rosea* roots (1.5-5:1) The trial received approval from the South East Coast, Brighton and Sussex Research Ethics Committee, the University of Surrey Committee of ethics and the Medicines and Healthcare Products Regulatory Agency (MHRA).

Participants and procedure. Students were screened for inclusion and if eligible were randomized to either the treatment (*Rhodiola rosea* L) or control group. The study had four phases. The baseline visit and completion of the validated baseline questionnaires and cognitive tests took place between 7 AM and 8 AM (Time 1 = T1). Following the baseline measures the experimental group received their first intake of the IMP. Dosing took place 30 min before breakfast, and another dose took place 30 min before lunch. Participants revisited the laboratory 4 h later on the same day (T2) and completed the same batch of questionnaires and cognitive tests (apart from the sleep measure). They returned to the laboratory again at 7 days (T3) and at 14 days (T4) and completed the same questionnaires and cognitive tests. Participants in the treatment group were telephoned each day to check IMP compliance, whilst participants in the control condition were telephoned to remind them of their next visit the day before their visit. To monitor compliance, participants were asked to bring back their used study medication packets. Participants were compensated for their time and were informed that they could voluntarily discontinue participation in this study at any time.

Inclusion criteria. In order to satisfy the inclusion criteria participants (1) had to be able to read, understand and sign the Informed Consent Form, and understand study procedures; (2) had to be healthy (on the basis of medical history, vital signs and the results of routine laboratory tests), male or female aged 18–35 years inclusive; (3) had reported a screening score above 30 on the STAI; (4) agreed to use suitable methods of contraception during the study and for 3 months afterwards; and (5) were non-smokers.

Exclusion criteria. Participants were not eligible for the study if (1) they were pregnant or breast feeding; (2) were consuming more than five caffeine-containing beverages per day; (3) were colour blind; (4) received clinically significant hepatic or renal abnormality as determined by laboratory tests; (5) had a BMI above 33; (6) had a history of alcohol, narcotic, benzodiazepine, or other substance abuse or dependence within the 12 months preceding; (7) had a positive alcohol breath test at any visit; (8) used any other medication which may interfere with study outcome and/or interfere with IMP within the 2 weeks or five half-lives preceding the first treatment phase; (9) currently participated in another clinical trial with an investigational or non-investigational drug or device, or participated in another clinical trial within the 3 months preceding Visit 1 (screening visit); or (10) had any condition that could compromise the subject's ability to meet protocol requirements or to complete the study.

[1]The international brand name in most countries is Vitango®. The product is manufactured by Dr Willmar Schwabe GmbH & Co. KG.

Primary outcomes measures

Anxiety. Anxiety was assessed using the STAI. This measure has 20 items each scored on a scale of 1 ('almost never') to 4 ('almost always'), which relate to how patients feel generally. Some items are specific to anxiety (e.g. 'I feel nervous and restless'), and others relating to more general symptoms of psychological distress (e.g. 'I feel like a failure') (Spielberger, 1983).

Stress. Stress was assessed using the Perceived Stress Scale (Cohen *et al*., 1994; Cohen *et al*., 1995). This is the most widely used and cited psychological instrument for measuring perception of stress. Participants rate the degree to which situations in their life are appraised as stressful using a 5-point scale (0 = Never, 1 = Almost Never, 2 = Sometimes, 3 = Fairly Often, 4 = Very Often), e.g. 'In the last month, how often have you been upset because of something that happened unexpected?'

Secondary outcomes measures

Mood. The Profile of Mood States Inventory (McNair *et al*., 1971) was employed to assess mood. This is a widely used measure of affective state, particularly appropriate for assessing fluctuations in mood. It comprises 65 items that measure six mood factors. These subscales assess (a) depression–dejection, (b) tension–anxiety, (c) anger–hostility, (d) confusion–bewilderment, (e) fatigue–inertia and (f) vigour–activity. Each item is an adjective describing a mood or feeling for which the participant has to indicate on a 5-point Likert-type scale the extent to which they are experiencing that feeling, i.e. not at all (0) to extremely (4). The Profile of Mood States yields six subscale scores and a total mood score, labelled total mood disturbance, which is derived from totalling the six subscales. The vigour subscale carries a negative weighting because it is the only positive mood characteristic.

Sleepiness. The Milford Epworth Sleepiness Scale (Johns, 1992) was used to assess daytime sleepiness. Sleepiness is assessed using a visual analogue scoring technique. Participants are required to rate their likelihood of them falling asleep in a number of everyday situations, and their overall mean score gives a measure of daytime sleepiness.

Sleep. The Leeds Sleep Evaluation Questionnaire (LSEQ) assesses the effects of psychoactive compounds on sleep and early morning behaviour (Parrott and Hindmarch, 1980). Participants mark a series of 100 mm line analogue scales, indicating the direction and magnitude of any changes in behavioural state they experience following administration of the drug. More specifically, the LSEQ considers the perceived ease of going to sleep, the quality of sleep, and any hangover effect the following morning. Scores are represented in millimetres.

Cognitive tests. Simple reaction time. Simple reaction time was measured using a computer-based task. Participants looked at a blank computer screen. When the word 'YES' appeared they responded by pressing a button as quickly as possible.

Choice reaction time. Choice reaction time was measured using a computer-based task. Participants looked at a blank computer screen and responded quickly to a word, but for this task there is a choice of words. The participant was instructed to press one button when the word YES appears and a different button when the word 'NO' appears.

Sustained Attention to Response Test (SART). The SART measures concentration. Participants sat at a computer, whilst numbers between one and nine appeared on the screen at a regular pace in a random order. They pressed the number on the keyboard corresponding to each number as it appeared on the screen. However, they were asked not to respond to the number '3'. The number of mistakes made indicates their tendency to drift off into an automatic, error prone style of responding as they lose concentration.

Symbol Digit Processing. Symbol digit processing measures speed of thinking. Participants were shown a key on the computer screen linking nine nonsense symbols with the numbers one to nine. Beneath the key, these symbols were displayed one at a time in a random order. The aim of this task was to press the number corresponding to the symbols as quickly and as accurately as possible.

Statistical analysis. Between groups characteristics were assessed by *t*-tests and chi-squared tests. Subjective questionnaire measures and cognitive tests were analysed using repeated measures analysis of covariance with group (treatment/control) as between group factors and testing session as the within subject factor, controlling for baseline scores. Where significant interactions were found these were broken down using *t*-tests in a series of planned comparisons. Cognitive performance was analysed as mean response latencies and percentage of errors.

RESULTS

As shown in Table 1, there was no significant difference between the groups on any of the demographic characteristics. In total, 216 students were screened for inclusion into the study of which 81 were randomized into one of two conditions: treatment = 40; control = 41 volunteers. Compliance was 100% for the treatment group. Every individual presented with a negative alcohol breath test over each of the testing phases. During the study, one participant in the treatment group terminated the study prematurely because of concomitant medication. As this individual had no measurement during the active study period, she was excluded from the analyses of effectiveness measures, but was analysed with regard to safety measures [adverse events (AE)]. Forty-one subjects were in the non-dosing arm (control group).

Table 1. Demographic data (frequency and *p*-values of the two-tailed χ^2-test or mean (SD), and *p*-value of the two-tailed *t*–test respectively)

	Rhodiola rosea L. (Vitano®)	Control	*p*
Sex Male	19	13	0.09
Female	20	28	
Age (years)	21.21 (2.46)	21.17 (3.03)	0.95
Height (cm)	173.02 (8.32)	170.92 (9.11)	0.28
Weight (kg)	67.89 (10.75)	64.41 (9.38)	0.12
Hip (cm)	98.76 (7.09)	98.12 (5.56)	0.65
Waist (cm)	78.23 (7.66)	75.87 (6.94)	0.15
Hip-to-waist ratio	0.78 (0.05)	0.77 (0.04)	0.21
BMI	22.59 (2.56)	22.00 (2.42)	0.30

Of the 40 subjects that were randomized to treatment (dosing) group, 4 subjects reported one treatment emergent AE each. Reported AEs were observed within several system organ classes (SOC). The reported event 'forgetfulness,' which was assigned to the SOC 'Nervous system disorder' as well the event 'loss of appetite' attributed to the SOC 'Metabolism and nutrition disorders', were known symptoms of the condition under investigation. The two other events 'food poisoning' (SOC 'Gastrointestinal disorders') and 'pelvic infection' (SOC 'Infections and infestations') seemed to be because of an independent concomitant condition. For two participants of the control group one AE was recorded in each case. For one subject who reported numbness and slight tingling in his left little finger, the preferred term was 'hypoaesthesia', this incident was coded within the SOC Nervous system disorders. In the second subject the event 'increased stress' attributed to the SOC 'Psychic disorders' was because of an independent exaggeration of everyday stress.

Primary outcome variable

Significant interaction effects were found for both Anxiety and Stress (Table 2). Relative to the control group, and controlling for baseline ratings, the treatment group showed a significant reduction in anxiety at T4, ($p < 0.01$), and a reduction in anxiety that approached significance at time T3 ($p = 0.08$), but there was no difference in ratings of anxiety between the groups at T2. For perceived stress the treatment group showed a non-significant trend to report less stress at T2, ($p = 0.08$), and T3 ($p = 0.06$), but reported significantly less stress at T4 ($p < 0.01$), relative to the control group. There were also main group effects with the treatment group reporting lower levers of anxiety and stress relative to the controls. Thus, both self-reported anxiety and perceived stress were significantly reduced in the treatment group.

Secondary outcome variables

With respect to the other mood factors, there were significant main group effects for Confusion, Depression

Table 2. Results, means (SD), and *p*-value for self-reported Stress and Anxiety for the Control and Vitano® groups

Measure	T1	T2	T3	T4	Time *F-value*	Group *F-value*	G × T *F-value*
Anxiety							
Control	41.68 (7.61)	38.85 (7.37)	40.60 (9.57)	41.44 (9.43)	0.70	5.02*	3.06*
Vitano®	40.24[a](6.71)	37.33 (7.13)	37.07 (7.65)	35.81[a](7.92)			
Stress							
Control	18.78 (5.82)	18.68 (5.96)	19.14 (6.83)	18.97 (6.68)	2.56	7.11**	4.33**
Vitano®	17.69[a](6.58)	16.68 (5.80)	16.43 (6.44)	15.25 [a](5.35)			

Values on each line sharing the same superscript were significantly different from one another.
*$p = <0.05$.
**$p = <0.01$.

and Total Negative Mood. In each case, this was due to lower ratings of Confusion, Depression and Total Negative Mood for the treatment group. Significant interaction effects were found for ratings of Anger, Confusion, and Total Negative Mood. Relative to the control group, and controlling for baseline ratings, the treatment group showed a significant reduction in anger at time T4 ($p < 0.05$), but there was no difference in ratings of anger between the groups at T2 and T3. For Confusion, the control group gave higher ratings at T4 ($p < 0.01$), but there was no difference in ratings of confusion between the groups at T2 and T3. For Total Negative Mood relative to the control group, and controlling for baseline ratings, the treatment group also gave lower ratings of Total Negative Mood at T4 ($p < 0.01$). No significant effects were found for the affective states of fatigue and tension.

Thus, the treatment (Vitano®) group demonstrated lower significant ratings of self-reported anger, confusion, and depression relative to the controls and showed significant improvements in total mood, over the course of the study. The analysis of the three sleep subscales revealed no significant differences between the two groups, and this was probably because of the participants reporting good sleep at baseline. Daytime sleepiness did not differ between the two groups (Table 3).

Table 3. Results, means (SD), and *p*-value for self-reported mood, sleep and sleepiness for the Control and Vitano® groups

Measure	T1	T2	T3	T4	Time *F-value*	Group *F-value*	G × T *F-value*
Anger							
Control	16.8 (4.07)	15.8 (4.33)	17.3 (5.99)	17.0 (5.70)	0.33	1.39	4.61*
Vitano®	16.4[a](4.20)	15.4 (4.62)	16.3 (5.12)	15.0[a](3.75)			
Confusion							
Control	13.1 [a] (3.80)	12.4 (3.82)	12.6 (4.70)	13.6 [a] (4.42)	0.60	7.40**	3.05*
Vitano®	12.7 (4.0)	11.5 (3.73)	11.2 (4.01)	11.0 (3.63)			
Depression							
Control	22.0 (5.94)	21.1 (5.75)	23.0 (8.90)	23.1 (7.10)	1.74	6.11**	2.25
Vitano®	22.8 (7.98)	20.4 (5.66)	20.8 (6.74)	19.6 (6.26)			
Fatigue							
Control	15.5 (4.86)	13.0 (3.77)	12.5 (4.90)	13.5 (5.15)	0.68	2.48	0.68
Vitano®	16.0 (5.78)	12.6 (4.59)	12.1 (4.85)	11.9 (4.73)			
Tension							
Control	14.5 (3.24)	14.2 (3.67)	15.0 (4.74)	14.5 (3.89)	1.56	3.45	0.56
Vitano®	15.5 (4.57)	14.0 (4.06)	13.9 (3.75)	13.9 (4.30)			
Vigour							
Control	17.8 (4.77)	20.4 (5.32)	20.9 (5.08)	21.0 (5.80)	4.03*	1.55	0.67
Vitano®	18.5(4.97)	21.2 (5.17)	21.7 (5.03)	22.8 (5.08)			
TNMood							
Control	112.0(19.1)	104.2 (11.4)	107.8 (27.4)	108.9 (23.1)	0.86	6.93**	4.90*
Vitano®	113.1[a](23.1)	106.8 (18.8)	100.7 (21.2)	98.2 [a] (18.2)			
Sleepiness							
Control	8.21 (3.57)	7.85 (4.02)	7.56 (3.78)	8.04 (4.78)	3.51*	0.01	2.52
Vitano®	7.05 (3.59)	7.30 (3.79)	6.76 (3.44)	6.41 (3.69)			
Sleep Qual							
Control	4.95 (1.45)		4.94 (1.43)	4.94 (1.28)	0.91	0.32	0.36
Vitano®	4.77 (1.22)		5.02 (1.44)	5.17 (1.73)			

Values on each line sharing the same superscript were significantly different from one another.
TNMood, Total Negative Mood; Sleep Qual, Sleep Quality.
*$p = <0.05$.
**$p = <0.01$.

Table 4. Results, means (SD), and *p*-value for the cognitive tests for the Control and Vitano® groups

Measure	T1	T2	T3	T4	Group *F-value*	G × T *F-value*
Simple reaction						
Time (ms)						
Control	387.00 (64.42)	378.15 (50.51)	383.11 (58.32)	386.22 (51.72)	0.05	0.26
Vitano®	372.48 (34.11)	368.98 (43.59)	375.17 (37.54)	374.89 (41.60)		
Choice Reaction						
Time (ms)						
Control	506.60 (73.81)	488.73 (65.03)	486.95 (64.96)	507.91 (77.63)	1.18	2.93
Vitano®	491.18 (64.51)	481.58 (59.25)	481.92 (59.23)	475.58 (52.76)		
SART (%ge correct)						
Control	89.30 (13.06)	89.93 (17.82)	95.33 (5.39)	95.50 (5.29)	1.50	0.78
Vitano®	92.40 (8.56)	94.05 (6.13)	95.55 (4.06)	94.07 (7.64)		
Symbol						
Digit						
Coding (%ge correct)						
Control	94.78 (4.57)	93.97 (5.19)	95.30 (4.51)	93.94 (8.20)	1.15	0.70
Vitano®	92.91 (7.66)	94.02 (4.83)	94.59 (5.78)	95.79 (4.67)		

$^{*}p = <0.05$, $^{**}p = <0.01$.

Cognitive tests

The performance on each of the cognitive tests is presented in Table 4. There was no difference in simple reaction times, choice reaction times, the mean number of errors on the SART, or errors on the symbol-digit coding task between the Vitano® group and control group. Thus across a range of cognitive tests no reduction in cognitive processing was found in the treatment group.

DISCUSSION

The purpose of this feasibility study was to evaluate the impact of *Rhodiola rosea* L extract (Vitano®) on self-reported stress and anxiety and concomitant mood symptoms in healthy individuals with mild anxiety. Following 14 days, the treatment group demonstrated a significant reduction in self-reported anxiety and stress. This finding supports previous evidence and research (Darbinyan *et al*., 2000; Panossian *et al*., 2010; Spasov *et al*., 2000; Darbinyan *et al*., 2007; Sarris, 2007). Although *Rhodiola rosea* has been used traditionally to relieve a range of symptoms of stress related disorders, to our knowledge this is the first study to demonstrate the efficacy of *Rhodiola rosea* L. in the treatment of mild anxiety.

Regarding the secondary measures, the analyses revealed significant reductions in self-reported Anger, Confusion, Depression and Total Negative Mood in the treatment group. These findings are interesting in particular as the participants were recruited solely on their anxiety scores and not other measures of mood. Vitano® appeared therefore to have a general positive effect on mood.

With regard to the cognitive tasks, no relevant differences between the groups could be observed. Vitano®, therefore appears not to affect cognition. In addition, consistent with previous research (Darbinyan *et al*., 2000; Darbinyan *et al*., 2007; Panossian and Wagner, 2005) none of the AEs were seen to be clearly related to intake of the treatment, because other reasons were more likely to be the cause, which suggests that *Rhodiola rosea* L. (Vitano®) can continue to be considered to have an adequate safety and tolerability profile, with a positive benefit-risk ratio.

Mood measures and sleep were assessed by self-report, and this could be considered a limitation to the study. Future research is needed to replicate the current findings, and it would be desirable to supplement the subjective nature of self-reports with more objective indices. Clinical interviews could be used to assess mood, and sleep could be assessed via wrist actigraphy or EEG. The lack of placebo control is another limitation of this study. It is unlikely that the findings were the result of placebo effects, as changes appeared gradual and were specific to certain measures. As this was a non-placebo RCT, however, we cannot determine a causal relationship, and we cannot exclude that some of the changes were because of time alone or other factors.

Overall the results demonstrated that *Rhodiola rosea* L. (Vitano®) is effective in the treatment of mild anxiety and stress. It improved confusion, anger, and total mood, and was well tolerated.

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Conflict of Interest

The authors declare no conflict of interest.

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