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Eleutherococcus senticosus reduces cardiovascular stress response in healthy subjects: a randomized, placebo-controlled trial

F. Facchinetti,* I. Neri and M. Tarabusi

Department of Gynecology Obstetrics and Pediatric Sciences, University of Modena and Reggio Emilia, Italy

Summary

The number of studies devoted to the scientific evaluation of phytotherapy is rapidly increasing since Western patients seem more oriented towards so-called 'alternative medicine'. Bearing such arguments in mind we decided to address attention to Eleutherococcus senticosus, *a root of the Ginseng family known for thousands of years in China as a remedy for psychological distress. Forty-five paid, healthy volunteers (20 males, 25 females) were recruited. Entry criteria were: good health, age 18–30 years, student and a Symptoms Rating Test score <10. At screening evaluation subjects were randomized to receive orally either placebo (Pl group) or Eleutherococcus senticosus (Es group) for 30 days, in a double-blind design. Subjects were submitted to a stressful cognitive task, the Stroop Colour–Word test (Stroop CW), both before and after treatment. Stroop CW increased heart rate (HR) and systolic BP in every subject. In females there was a greater response than in males in terms of both systolic and diastolic BP. For both genders, the HR response to Stroop CW was reduced by Es treatment while no changes were found after Pl. In females, systolic BP was also reduced in Es group while it remained unchanged in Pl group. This study demonstrated that treatment with Eleutherococcus senticosus is able to reduce cardiovascular responses to stress in healthy young volunteers, while placebo was ineffective. Eleutherococcus senticosus is confirmed to be helpful for stress adaptation.*

Key Words

stress; cardiovascular response; Eleutherococcus senticosus; complementary medicine; sex dimorphism

Introduction

Chinese traditional medicine is entering the Western medical world very rapidly. The number of studies devoted to scientific evaluation of acupuncture and phytotherapy is rapidly increasing since patients seem more oriented towards so-called 'alternative medicines' because they have found them more congruent with their own values.[1] There are a group of so-called tonic remedies in Far Eastern medicine, which are traditionally viewed, as harmonizing or adjustive. Ginseng and Eleutherococcus are the best known, and there is evidence that they increase arousal, stamina and stress resistance. We have attempted to explore the relationship between the behavioural and stress effects, and to relate this to traditional concepts.[2] The experiments performed on emotional-painful stress

* Correspondence to: F. Facchinetti, Dipartimento di Scienze Ginecologiche, Ostetriche e Pediatriche, via del Pozzo 71, 41100 Modena, Italia.
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model in rats demonstrated the cardio-protective activity of adaptogens of vegetables origin (rodiolae, eleutherococcus levsea, p-tyrosol).[2] The cardioprotective effect of adaptogens prevents stressor-induced changes in the level of cyclic nucleotides in the myocardium. Bearing such arguments in mind we decided to address our attention to the *Eleutherococcus senticosus*, a root known for thousands of years in China as remedy for psychophysical stress. It is active in stimulating arousal and supporting mental efforts.[3] Therefore, we have undertaken a randomized, placebo-controlled, clinical trial in order to verify the above-reported proprieties of *Eleutherococcus senticosus* in healthy volunteers.

Material and methods

Subjects

Forty-five paid, healthy volunteers (20 M and 25 F) were recruited among 55 students who applied for enrolment. Entry criteria were: good health, age 18–30 years, student and a Symptom Rating Test (SRT) score <10, meaning the absence of psychological distress. SRT is a test that measures psychological distress and is composed of four subscales: anxiety, depression, somatization and sense of inadequacy.[4] Subjects with SRT $>$ 10, using psycho stimulants, pregnant women or women exposed to pregnancy, and subjects taking any other drug were excluded. At screening evaluation, informed consent was obtained and subjects were randomized to receive either placebo (Pl) or *Eleutherococcus senticosus* (Es) (Fon Wan Blu Giuliani, Milan, I; 2 vials/day), for 30 days, in a double-blind design. The mean age of the two groups were 24.2 ± 2.1 and 25.1 ± 2.6 years respectively. The male/female mean ages were $24.5 \pm 2.5/24.8 \pm 1.6$ years and $23.9 \pm 3.3/25.1 \pm 2.5$ years, respectively in the two groups.

Testing

The Stroop Colour–Word test (Stroop CW) was used as a challenge stressor before and after treatment. Stroop CW is an experimental situation that has been used for years to examine attention and other cognitive processes.[5] Facchinetti *et al.* in two previous studies[6,7] utilized the Stroop CW as a test for measuring stress reactivity.

Subjects were asked to read three consecutive sheets, having 45 s to complete each one. The first one contained 100 words (red, blue, yellow, green) written in black ink to be read as quickly as possible, giving the score W; the second sheet contained 100 spots of the four colours mentioned above to be read, giving the score C. In the latter, the four words red, blue, yellow and green were printed in incongruent colours, and the task was to ignore the word and name as many colours as possible, giving the score CW. At each mistake subjects stopped, corrected and start reading again. Each subject was expressly instructed to read as many words, colours and colour-words as possible. The investigator stressed the importance of the performance to the subjects by telling them that the number of words and colours they read was directly related to their ability to cope with stress. At the end of the session, the subjects remained seated for a further 10 min. Using an automated blood pressure device (Dinamap; Critikon, Milan, Italy), systolic BP, diastolic BP and heart rate (HR) were measured three times before testing (baseline), once after reading each sheet and again three times after the end of testing (recovery). To measure the peak cardiovascular response, measurements started at the 20th second during the reading of each sheet. Both baseline and recovery measures were averaged.

Statistical analysis

The analysis of cardiovascular responses to Stroop CW was carried out using multiple analyses of variance for repeated measures. Moreover, the Percentage Total Change (PTC) was calculated by adding the percentage changes over baseline at different times during Stroop CW, for every parameter. PTC values were compared by treatment or by sex using either paired or unpaired *t*-tests.

Results

In the resting condition before any treatment had been started cardiovascular parameters were within normal range. However, systolic BP values in males (118.3 ± 10.6 mmHg) were significantly higher than in females (104.7 ± 11.6 mmHg $p = 0.0002$) and to a lesser extent, also diastolic BP was higher in males (63.8 ± 9.3 mmHg) than in females (58.0 ± 10.2 mmHg $p = 0.05$). Every subject solved Stroop CW text. The name of colour/words read on the third page was similar in males (51.4 ± 13.0) and females (50.3 ± 11.3).

Before treatment subjects reacted to the Stroop CW stimulation with an increase in both systolic BP (from 110.8 ± 13.0 to 121.2 ± 10.8 mmHg; MANOVA: df = 176, $F = 46.3, p =< 0.001$) and HR (from 68.2 ± 10.9 to 77.2 ± 13.1 b.p.m.; MANOVA: df = 176, $F = 53.9, p =< 0.001$). Diastolic BP (MANOVA: df = 176, $F = 34.4, p =< 0.001$) was also stimulated, but at a lower magnitude than systolic BP.

The gender differences in baseline BP values and Stroop CW reaction before treatment were analysed separately for both males and females (Table I). On several occasions during stimulation, systolic and diastolic BP changes in males were consistently higher than those in females while heart rate values did not differ. However, a comprehensive view of the reaction to Stroop CW calculated as PTC was higher in females than in males for both systolic BP (female 43.2 ± 24.7 per cent; male 21.7 ± 22.0 per cent; $p = 0.004$) and diastolic BP (female: 59.6 ± 40.5 per cent; male 28.4 ± 35.0 per cent; $p = 0.009$), whereas the response of HR was similar between sexes.

In males after placebo treatment Systolic BP reactions to Stroop CW disappeared and values measured during the test were consistently lower than those recorded at baseline (Table II). No placebo effect was observed on either diastolic BP or heart rate. In females, placebo partially attenuated the reaction of systolic BP ($F = 11.9, p < 0.001$) and diastolic BP ($F = 5.8, p < 0.001$) to Stroop CW, although the HR response was still present.

The comprehensive responses to placebo are reported in Figures 1 and 2 where a significant placebo effect on systolic BP was observed only in males. The cardiovascular reaction to Stroop CW before and after active treatment are detailed in Table III. In males treatment with *Eleutherococcus senticosus* resulted in a reduced response of both systolic BP and heart rate to the Stroop CW with respect to baseline values (Figure 1). A similar finding was obtained also in females (Figure 2).

After placebo, males showed a reduced reaction of systolic BP compared with females (27.4 ± 18.0 per cent, $p = 0.01$). In contrast, the effect of *Eleutherococcus senticosus* in reducing HR response to Stroop CW was similar in both males (35.8 ± 1.6 per cent) and females (29.9 ± 7.9 per cent) (Figures 1 and 2).

Discussion

This randomized, placebo-controlled trial demonstrates that treatment with *Eleutherococcus senticosus* is able to reduce cardiovascular response to stress in healthy young volunteers. In particular, 30 days of oral treatment reduced the heart rate reactivity to a cognitive task such as the Stroop CW to about 40 per cent in both males and females, while placebo was ineffective. Females also reported a 60 per cent reduction in systolic BP response whereas in males this parameter was reduced to the same extent even after placebo.

Despite the placebo-controlled design of this study one could argue that post-treatment responses would depend on an habituation effect. This issue was addressed by Guerra *et al.*[8] who exposed 20 subjects to a battery of stress tasks, including Stroop CW, twice in a 8-day period. The results demonstrated that both heart rate and systolic BP, in direct correlation with catecholamines, increased during the first session and were not affected by

Table I. Systolic blood pressure (BP), diastolic BP and heart rate responses to Stroop CW according to gender.

	Baseline	First sheet	Second sheet	Third sheet	Recovery
Systolic BP					
Male	$118.3 \pm 10.6^*$	127.0 ± 12.1	127.5 ± 7.7	124.2 ± 7.6	118.3 ± 8.7
Female	104.7 ± 11.6	118.4 ± 11.8	119.2 ± 14.4	118.8 ± 12.4	106.2 ± 10.0
$P =$	0.0002	0.02	0.02	N.S.	0.0001
Diastolic BP					
Male	63.8 ± 9.3	73.9 ± 10.1	69.2 ± 9.0	69.2 ± 8.6	60.2 ± 6.5
Female	58.0 ± 10.2	66.6 ± 11.6	70.0 ± 11.1	73.3 ± 9.9	58.9 ± 7.6
$P =$	0.05	0.03	n.s.	n.s.	n.s.
Heart rate					
Male	68.1 ± 12.6	85.4 ± 13.0	76.9 ± 13.4	75.2 ± 14.3	69.5 ± 10.4
Female	68.2 ± 9.5	83.7 ± 14.2	78.4 ± 12.1	78.8 ± 12.0	68.9 ± 8.9
$P =$	n.s.	n.s.	n.s.	n.s.	n.s.

P refers to within-subjects statistical significance. n.s., not significant; *mean ± SD.

Table II. Systolic blood pressure (BP) diastolic BP and heart rate in males and females treated with placebo.

Placebo	Baseline	First sheet	Second sheet	Third sheet	Recovery
Males					
Systolic BP					
Baseline	120.8 ± 9.9*	128.3 ± 11.6	128.2 ± 6.5	124.4 ± 5.8	120.6 ± 10.7
Post-treatment	119.0 ± 10.1	119.0 ± 10.1	120.5 ± 12.2	117.6 ± 5.5	115.8 ± 7.1
$P =$	n.s.	n.s.	0.009	0.004	0.05
Diastolic BP					
Baseline	66.1 ± 10.0	75.3 ± 9.2	71.1 ± 8.6	69.2 ± 8.6	61.4 ± 5.9
Post-treatment	63.8 ± 8.7	67.1 ± 14.3	65.8 ± 10.6	69.8 ± 11.1	60.1 ± 10.6
$P =$	n.s.	0.02	n.s.	n.s.	n.s.
Heart rate					
Baseline	64.5 ± 11.3	81.2 ± 10.3	72.9 ± 10.1	72.0 ± 15.1	67.2 ± 8.4
Post-treatment	69.8 ± 10.6	77.9 ± 13.7	73.2 ± 10.8	71.6 ± 5.5	73.0 ± 11.4
$P =$	n.s.	n.s.	n.s.	n.s.	0.03
Females					
Systolic BP					
Baseline	108.9 ± 9.1	120.2 ± 11.3	126.1 ± 14.1	121.7 ± 13.4	109.2 ± 12.4
Post-treatment	107.8 ± 8.7	118.6 ± 9.4	119.5 ± 15.5	113.1 ± 11	102.2 ± 9.4
$P =$	n.s.	n.s.	0.02	0.000	n.s.
Diastolic BP					
Baseline	62.6 ± 8.1	68.5 ± 6.9	74.9 ± 11.3	73.3 ± 9.9	63.3 ± 6.5
Post-treatment	62.2 ± 6.8	73.1 ± 13.8	69.6 ± 11.4	67.7 ± 14.9	63.0 ± 10.3
$P =$	n.s.	n.s.	0.01	0.03	n.s.
Heart rate					
Baseline	68.2 ± 12.3	80.1 ± 17.7	80.2 ± 14.8	79.5 ± 14.7	72.0 ± 15.1
Post-treatment	72.2 ± 7.2	82.7 ± 14.0	80.9 ± 11.3	78.0 ± 14.0	71.6 ± 5.5
$P =$	n.s.	n.s.	n.s.	n.s.	n.s.

P refers to within-subjects statistical significance. n.s., not significant; *mean ± SD.

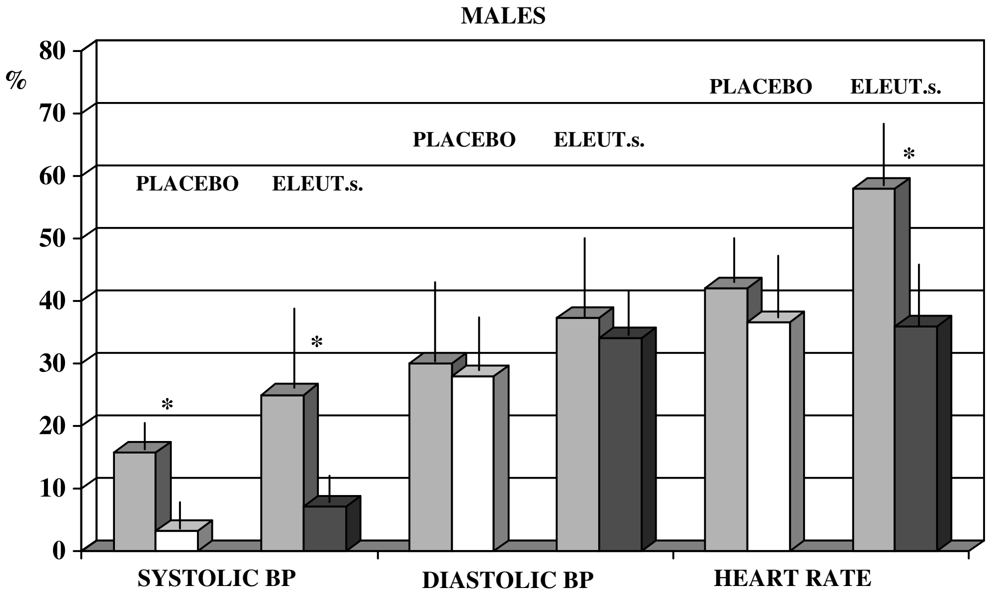

Figure 1. Responses ($M \pm$ SD) to Stroop CW as Percentage Total Change in males before (open bars) and after (hatched bars) treatment.

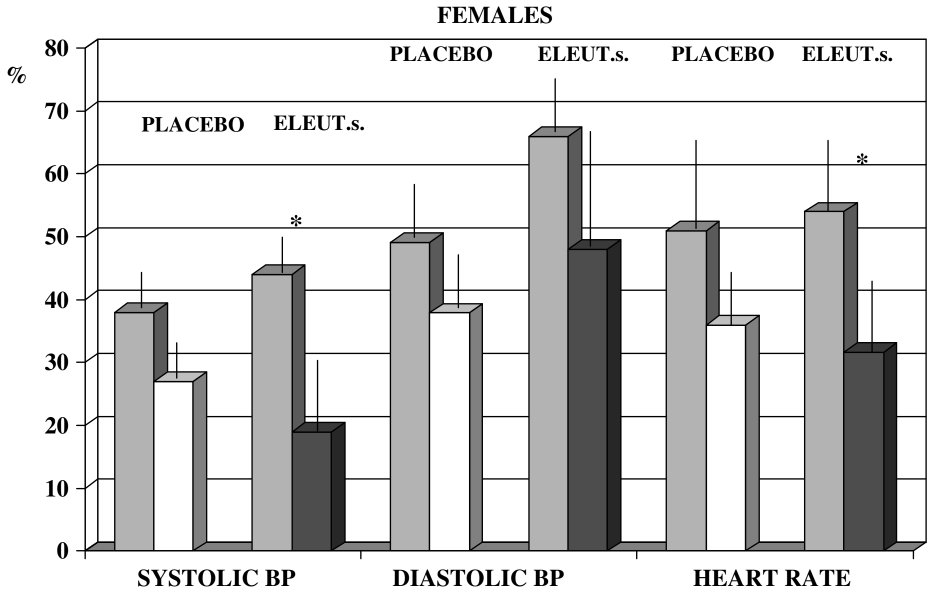

Figure 2. Responses ($M \pm$ SD) to Stroop CW as Percentage Total Change in females before (open bars) and after (hatched bars) treatment.

Table III. Systolic blood pressure (BP), diastolic BP and heart rate in males and females treated with *Eleutherococcus senticosus*.

Eleutherococcus senticosus	Baseline	First sheet	Second sheet	Third sheet	Recovery
Males					
Systolic BP					
Baseline	115.2 ± 11.3*	125.5 ± 13.2	126.7 ± 9.4	124.0 ± 9.8	113.7 ± 4.8
Post-treatment	119.4 ± 7.9	124.1 ± 8.1	121.5 ± 10.1	121.3 ± 9.2	115.7 ± 8.3
P =	n.s.	n.s.	n.s.	n.s.	n.s.
Diastolic BP					
Baseline	59.7 ± 9.6	72.3 ± 11.5	66.8 ± 9.5	66.3 ± 8.5	57.2 ± 7.4
Post-treatment	62.7 ± 8.5	73.6 ± 7.9	70.4 ± 8.4	65.5 ± 10.9	58.3 ± 7.8
P =	n.s.	n.s.	n.s.	n.s.	n.s.
Heart rate					
Baseline	70.3 ± 9.7	86.0 ± 12.9	79.6 ± 10.4	79.1 ± 10.1	72.8 ± 8.9
Post-treatment	69.8 ± 9.0	81.5 ± 9.1	76.0 ± 9.7	74.0 ± 8.6	69.1 ± 5.5
P =	n.s.	n.s.	n.s.	n.s.	n.s.
Females					
Systolic BP					
Baseline	101.1 ± 12.6	116.8 ± 12.4	112.8 ± 11.8	116.1 ± 11.2	103.5 ± 6.4
Post-treatment	104.2 ± 10.4	115.1 ± 7.3	114.0 ± 9.3	107.1 ± 12.4	105.5 ± 9.1
P =	n.s.	n.s.	n.s.	0.01.	n.s.
Diastolic BP					
Baseline	53.8 ± 10.4	64.9 ± 14.8	65.5 ± 9.0	63.5 ± 10.1	55.0 ± 6.4
Post-treatment	55.9 ± 8.4	70.1 ± 5.1	62.7 ± 7.4	59.9 ± 9.7	56.1 ± 5.8
P =	n.s.	n.s.	n.s.	n.s.	n.s.
Heart rate					
Baseline	68.2 ± 6.7	87.1 ± 9.6	76.8 ± 9.1	78.1 ± 9.4	68.6 ± 6.3
Post-treatment	70.9 ± 7.4	87.1 ± 11.3	74.1 ± 10.4	72.8 ± 8.6	71.1 ± 6.9
P =	n.s.	n.s.	n.s.	0.01	n.s.

P refers to within-subject statistical significance. n.s., not significant; *mean ± SD.

habituation in the second. In our study, it can therefore be concluded that the attenuation of the heart rate (and also systolic BP in females) response to stress was a genuine effect of the alleged properties of *Eleutherococcus senticosus*. The significant response of systolic BP after placebo remains to be explained.

This plant belongs to the same family as *Panax ginseng* and the extract of its roots is traditionally believed to restore energy and to improve concentration and the ability to work efficiently.[9] In other words, *Eleutherococcus senticosus* could be considered to be coping stimulator. The data of our study strongly supports such an action. Like other ginseng roots it also exerts tonic effects on physical strain. Pre-treatment with *Eleutherococcus senticosus* reduced the lactic acid levels in rats which had been exposed to a 2-h swimming task and also increased survival in rats exposed to very low-temperatures.[3] Moreover, several reports in Eastern literature confirm that exposure to *Eleutherococcus senticosus* increased attention in professionals, allowing to function more effectively.[10]

Interestingly, female students seem to benefit more than males from the adaptive properties of *Eleutherococcus senticosus*. Such gender-related difference could be associated with the different impact gonadal steroids have on the hypothalamus–pituitary–adrenal axis. In resting conditions, our population of male subjects showed higher systolic and diastolic BP values than females and this finding confirms previous observations on adrenaline levels and platelet alpha-adrenoceptors content[11] as well as on the ACTH response to psychosocial stress.[12] Moreover, during the first session, before any treatment had began, female students reacted to Stroop CW with a higher increase in both systolic and diastolic BP than male colleagues, while activation of the heart rate was similar in both sexes. Males respond more to 'male challenges' and females respond more to 'female challenges'. It is possible that the way in which the task was introduced may have induced more fear in females than in males. However, controversies regarding gender-related differences in response to experimental stress have been reported.[13] Using another cognitive task, Earle *et al.*[14] reported that males had a higher reactivity in terms of cortisol and diastolic BP changes while females showed a greater heart rate response than males. In contrast, Litschauer *et al.*[11] were unable to find any differences in adrenergic response to Stroop CW between the sexes. Such controversies could also be explained by the fact that there are several determinants of experimental stress reactivity such as age,[15] personality features,[16] interaction of the task with social values, in addition to coping ability[17,18] and negative emotions.[14] Possibly, experimental-induced stress is a stimulus whose response depends more on the above-mentioned factors than on sex difference, if any.

In any case, this randomized, placebo-controlled trial supports the traditional belief that *Eleutherococcus senticosus* is helpful for stress adaptation.

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