No Benefit Adding *Eleutherococcus senticosus* to Stress Management Training in Stress-Related Fatigue/ Weakness, Impaired Work or Concentration, A Randomized Controlled Study

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Key words
- adaptogens
- Siberian ginseng
- *Eleutherococcus*
- asthenia
- stress
- RCT
- fatigue
- concentration

Abstract

Introduction: Plant adaptogens are traditionally used for stress-related symptoms, but clinical evidence is inconsistent. This trial explored the effects of 120 mg/day *Eleutherococcus senticosus* root extract (ES), 2-day professional stress management training (SMT) and a combination of both (COM).

Methods: 144 participants suffering from asthenia and reduced working capacity related to chronic stress were randomized to the treatments. Validated scales and tests were used to investigate cognitive performance; feeling stressed; fatigue and exhaustion; alertness, restlessness and mood; quality of life and sleep; physical complaints and activities; and physiological stress parameters including cortisol awakening response (CAR), at baseline, after 2 and 8 weeks of treatment (German Clinical Trials Register DRKS00000692).

Results: Almost all parameters improved significantly over time without group differences. Significant differences were found in mental fatigue and restlessness, both in favor of COM vs. ES. COM was not superior to SMT in any parameter at week 8. An attenuation of the CAR was seen at week 2 without group differences. All treatments were well tolerated.

Discussion: Effects of adding ES to SMT are, if any, negligible.

Introduction

Strategies in chronic stress management include physical activity, cognitive training as well as psychological techniques for relaxation, concentration and self-organization, such as yoga, autogenic training, muscle relaxation, or biofeedback [1–5]. Relaxing and strengthening effects are also attributed to some plants like ginseng (*Panax ginseng*), Siberian ginseng (*Eleutherococcus senticosus*), roseroot (*Rhodiola rosea*) and Chinese magnolia vine (*Schisandra chinensis*) for which the term "adaptogens" has been suggested. Plant adaptogens have been conceptualized as herbal preparations which increase the ability of an organism to adapt to a wide variety of biological, chemical and physical environmental stressors and to avoid damage from such factors [6]; they are thought to be non-toxic, non-specific in their pharmacological action, to exert a normalizing effect on various organ systems the more pronounced as the deeper are the pathological changes in the organism [7]. In contrast to stimulants, adaptogens should cause an increase in working capacity and physical endurance which is not followed by a counter-regulating decrease, and other than in tonics their application is not restricted to conditions of asthenia. Numerous studies have investigated the effect of adaptogens on humans under extreme environmental conditions like high altitudes, arctic and tropic temperatures, submarines, long distance flights and in top-level sports [8]. Enhancement of basic cognitive, memory and sensory functions in acute and long-term studies, mitigation of chronic fatigue and immune-stimulating properties have been reported. Influences on the hypothalamic-pituitary-adrenal (HPA) axis and on mediators of stress response such as molecular chaperons are discussed as underlying mechanisms [9].

Ethanolic *Eleutherococcus senticosus* root extract (ES) is one of the most widely used and extensively investigated adaptogens. Although numerous studies with over 6000 participants have been performed on ES since the 1960s and the reports were generally positive, the assessment report of the EMA Herbal Medicinal Products Committee (HMPC) in 2008 concluded that "none of the studies would be sufficient to substantiate efficacy of ES preparations in a clearly

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defined clinical condition, although, in total, the data available are sufficient to justify further research into the concept of adaptogens". This is due to the fact that these studies have been conducted in a very wide range of clinical conditions with various instruments and for different efficacy parameters over a long period of time. Most studies do not meet modern clinical trial standards of Good Clinical Practice (GCP). Therefore the present investigation was designed to explore effects of taking the popular adaptogen ES in addition to non-pharmacological measures on a variety of cognitive, psychological and physiological parameters in a well-defined population of trial participants subjectively bothered by chronic stress, by applying validated test instruments in a modern GCP setting.

Since non-specific effects (e.g., regression to the mean) were expected to occur in this population, a randomized 3-arm study design was chosen comparing ES with a well-conducted professional stress management training (SMT) and a combination (COM) of both treatments. Effects of regularly taking ES would emerge from the comparison of COM with SMT, effects of SMT from the comparison of COM with ES, and additive or synergistic effects from the comparison of all 3 trial arms. As we were primarily interested in the clinical benefit of the treatment strategy "adding regular intake of ES", i.e., the sum of the unspecific benefit associated with the regular intake of a promising drug and pure pharmacological effects, we did not select a placebo control.

Methods

This multicentric, phase IV study was designed as a prospective, exploratory, open, controlled, randomized 3-arm parallel group comparison of 3 treatment schedules: (i) participation in a 2-day structured stress management group seminar (SMT); (ii) participation in the stress management seminar plus oral treatment with ES capsules (COM); (iii) oral treatment with ES capsules only (ES).

The study was conducted in compliance with the declaration of Helsinki, ICH-GCP, applicable laws and regulations. The protocol, informed consent documents and subject allowance were approved by the competent federal authority (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) and given a favourable opinion by the independent ethics committee of the Bavarian Medical Association (German Clinical Trials Register DRKS00000692, EudraCT 2010-022114-12), as applicable. The study was performed at 6 urban professional clinical trial outpatient units in Germany between January and July 2011.

Participants

Female and male, 30–50 year-old participants without somatic or psychiatric diagnoses requiring treatment or further medical examination, as confirmed by a board certified specialist after screening procedures, were recruited via newspaper advertisements or selected from a data pool kept by the research institutes. Specific inclusion criteria were: symptoms of asthenia such as fatigue or weakness indicated by a score >6 in at least one Multidimensional Fatigue Inventory (MFI-20 [10]) subscale, decline in working capacity and power of concentration with a score >8 in the subscale performance of the Change-sensitive Symptom List (ASS-SYM [11]), exposure to chronic occupational and/or social stress with scores >60 in at least 2 subscales of the "Trier Inventory for Chronic Stress" (TICS [12]). Subjects who had suffered from serious or acute systemic disease within 4 weeks, or had experienced an acute or chronic psychiatric (DSM IV axis I) or neurological disease or psychotherapy within 12 months prior to screening were not included. Concomitant medication with psychotropic drugs, hypnotics, anti-epileptics, Parkinson disease drugs, anaesthetics, muscle relaxants, centrally active analgesics/hypotensives/ antihistamines/antiemetics, cardiac glycosides, vitamin B preparations, phytomedicines or food supplements was not allowed. Participants with clinically relevant findings in ECG or laboratory parameters, insulin dependent diabetes mellitus, hypertension, internal diseases or conditions prohibiting participation in progressive muscle relaxation were not included.

Study procedures and interventions

Participants had to attend a screening visit (V1) to receive information about the study and give written informed consent, and for medical history, physical examination, documentation of demographic data, vital signs, ECG, safety laboratory, concomitant medication and check of in- and exclusion criteria (including questionnaires ASS-SYM, TICS, MFI-20 and Beck Depression Inventory BDI-II [13]). 3–28 days later visit 2 (V2) was scheduled when baseline safety and efficacy data were recorded and the trial participants were randomized 1:1:1 to either of the 3 treatment groups. Within 1–7 days from V2, participants allocated to SMT or COM had to attend a study specific 2-day structured stress-management group training, conducted by 4 experienced professional trainers based on a detailed manual, which included, e.g., education, cognitive stress management strategies, progressive muscle relaxation according to Jacobson and individualized strategies for future optimization of competences, resources and techniques to cope with stress (Wiblishauser Seminare, Haar, Germany). Before trial initiation trainers attended a study specific 1-day training with the manual author to familiarize with the manual and agree onto uniform conduct of the trainings. Treatment group COM (in addition to the anti-stress training) and group ES received 120 mg dry extract WS® 1070 (1 capsule) daily of Siberian ginseng root (Eleutherococci Radix), drug:extract ratio 16–25:1, extraction solvent 30% [v/v] ethanol, for 8 weeks. WS® 1070 was provided by the sponsor and funding source of the trial, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany. On visits 3 (day 12–16) and 4 (day 53–59) efficacy data, adverse events were recorded, saliva samples were collected, unused study medication was taken back and counted or new medication issued.

Objectives

Objectives of the study were to explore potential synergies between taking ES and structured SMT with respect to efficacy, and to assess safety and tolerability of ES alone or in combination with SMT in subjects with impaired working performance, concentration capability, fatigue and weakness patterns, and subjectively experiencing high stress levels.

Outcomes

Since this was an exploratory study, no distinction of primary and secondary efficacy parameters was made. The following areas were investigated using standardized and validated tests or scales:

Cognitive performance: Memory was tested with the Visual and Verbal Retention Test (VVM [14]) including memorization of

visual (path on a town map) and verbal (house construction details) information, both with immediate and delayed (1–2 h) recall. **Attention** was determined with the computerized Attention Test Battery (TAP [15, 16]) including the following tasks on working memory, divided attention (simultaneous visual and acoustic signals) and Go/NoGo (inhibition of fast reactions to critical visual signals), incompatibility (divergent stimulus information has to be processed in parallel in a conflict situation), and visual scanning (a critical stimulus must be detected in a matrix). **Concentration problems** were assessed by a questionnaire (KiA, [17]) comprising 100 questions on "concentration in everyday life".

Feeling stressed: The **subjective feeling of stress** was documented with the TICS comprising 57 items in 9 subscales: work overload, excessive social stress, pressure to succeed, dissatisfaction with work, excessive professional demands, lack of social recognition, social tension, social isolation, and continued concern. **Functional impairment** in work, social and family life was documented with the Sheehan Disability Scale (SDS [18]), a brief self-rating tool using a (100 mm) visual analog scale and asking for the number of lost and unproductive days.

Fatigue and exhaustion: **Fatigue** was assessed with the MFI-20, a 20-item self-report instrument covering the following dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. **Exhaustion** was rated using the subscale "exhaustion" of the ASS-SYM which determines changes in areas of problems and complaints responding to relaxation methods like autogenic training or progressive muscle relation.

Alertness, restlessness, mood: The Multidimensional Mood State Questionnaire (German version: MBDF [19]) uses 24 Likert scales to differentiate **good/bad mood**, **alertness/fatigue** and **calmness/restlessness**. In addition, **tension** and **self-determination** were assessed with the respective subscales of the ASS-SYM [11].

Depressive mood: **Depressive symptoms** were recorded with the BDI-II, rating 21 mental and somatic items.

Quality of life: The WHO-5 index [20] assesses **well-being** at the actual time by asking for the quality of mood, calmness, activity, sleep and interest within the last 2 weeks.
Sleep quality was determined with the Leeds Sleep Evaluation Questionnaire (LSEQ [21]), comprising 10 visual analog scales referring to getting to sleep, quality of sleep, awake following sleep and behaviour following wakening.

Physical complaints and activities: **Physical complaints** were recorded with the ASS-SYM [11] subscales "dysregulation" and "burden of pain". The Freiburg Questionnaire on Physical Activity (FFKA [22]) comprises 10 questions regarding time spent with different **physical activities** (basic activity, leisure activities, and sports).
All tests were performed at V2 (baseline) and V4 (week 8), and all except KiA, TICS and FFKA also on V3 (week 2).

Physiological stress parameters: **Heart rate variability** (HRV [23]) during neuropsychological testing (TAP) was defined as mean square of differences in consecutive interbeat intervals from ECG.

Electrodermal activity (EDA) was recorded during TAP with 2 electrodes with 0.5 volt applied to the palm of the non-dominant hand. Electrodermal reactions were defined as changes ≥ 0.02 µS. The following parameters were evaluated: mean dermal conductibility, frequency of electrodermal responses per min, and accumulated amplitude of spontaneous electrodermal responses over the test period [24]. **Salivary cortisol concentration** [25–27] was determined at 2 consecutive working days preceding each of the visits 2, 3, and 4. Subjects were instructed by investigators to sample salivary probes at the times indicated and to write the actual sampling time on the respective tube. Analysis of samples was conducted by a specialized certified lab, running internal standards with every measurement and participating in regular interlaboratory comparisons. 2 time profiles were measured: awakening profile immediately after waking up and after 30 and 45 min; the diurnal profile at 9 a.m., 3 p.m. and 9 p.m. The cortisol awakening response was calculated as difference between measurements at 30 min and awakening, the diurnal change as difference between 3 p.m. and 9 a.m.

Treatment satisfaction: At V3 and V4, participants should indicate (on Likert scales) their satisfaction with efficacy and safety of their treatments and their willingness to continue.
Investigators and site staff received a 1-day training on questionnaire administration and scoring, TAP application, and physiological measurements, conducted by 2 of the authors (OW, MB), the manufacturer of the HRV/EDA device, and a cortisol lab representative.

Sample size calculation and allocation procedure

Comparable investigations found pharmacological effects on stress-induced complaints in collectives of 30–40 trial participants per group [28–30]. For a sample of 105 evaluable subjects with 3 interventional groups and 3 assessment time points, 2-factorial ANOVA can detect effect sizes of 0.5 standard deviations with a power of 90%. Taking into account a 20% drop-out rate and 5 planned sites, 135 participants were planned to be included.
On visit 2 each participant was entered into a validated web-based randomization system (MARVIN, Xclinical, Munich, Germany) by trained study site personnel. Based on a random list generated with the program Rancode Professional 3.6 (idv, Gauting, Germany) by an independent biometrician not involved in any other study-related activities, the system allocated the patient to a treatment group. Participants were randomized by site in blocks of 3, according to a pre-specified written randomization plan. Investigators were unaware of the fact of randomization by site, the block size and the randomization plan throughout the trial.

Statistical evaluation

Because selective drop-out was expected between groups, missing values were replaced by multiple imputation. For multiple imputation, the parameters of the multivariate normal distribution of the respective endpoint were estimated by the expectation-maximization-algorithm with the NORM package for the statistics software R, based on the available data from the total study sample (not the respective treatment group). A missing value was randomly imputed, where the imputation was based on the estimated parameters and the observed values of the respective multivariate observation. This was repeated 5 times to generate 5 datasets for each variable. Efficacy analyses were

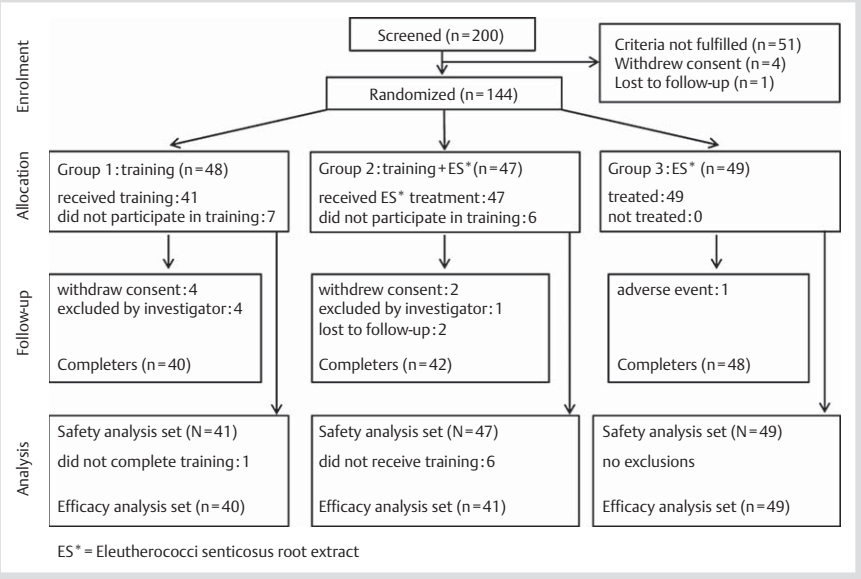

Fig. 1 Study flow chart.

conducted on each of these datasets and results were averaged. All efficacy parameters were evaluated for the intention-to-treat (ITT) analysis sets. The ITT population was defined as all participants having received at least one treatment with at least one post-baseline efficacy evaluation. Participants from group COM were only included into the ITT population if they had received both, ES and SMT. Because of the multiple imputation procedure, the number of subjects for whom at least one post-baseline efficacy evaluation was available or could be imputed differed slightly between endpoints. Therefore the ITT analysis sets were defined separately for each endpoint. Data were evaluated with descriptive methods. A significant treatment effect was defined as a group × visit interaction in 2-factorial analysis of variance for repeated measurements (ANOVA) with a p-value <0.05. In this case, effects were further analyzed by 1- (group) and 3- (group, visit, gender) factorial ANOVAs and by post-hoc unpaired t-tests with Welsh approximation. As this was an exploratory trial, no primary endpoint was selected and no correction for multiplicity of testing was applied. Therefore, reported p-values are descriptive. The numbers of adverse events were evaluated for the safety analysis set, i. e., all participants randomized that received treatment at least once. Statistical analysis was conducted with SPSS Statistics 18 and R software package, version 2.13.1.

Results

Study population

200 subjects were screened and 144 were allocated in randomized order to the 3 treatments groups (**Fig. 1**). Out of 48 participants allocated to group SMT, 7 did not and 1 person did only partially participate in the stress management seminar, so finally 40 were included in the efficacy analysis. Missing the seminar was also the only reason for exclusion from efficacy analysis in group COM (6 of 47), and 1 subject in group ES terminated early because of adverse events (dyspepsia and flatulence, probably not treatment-related). Stress management training was conducted in 15 2-day sessions with 3–9 participants/session.

Participants were Caucasians, exceptions being 1 Asian and 1 African person both in group COM. There were more women than men in this study (56.9% vs. 43.1%); the highest percentage of women was seen in group SMT (63.4%; group COM: 53.2%; group ES: 55.1%). Mean age was 41.2 ± 5.9 years (30–50) without significant differences between groups (group means 41.9/ 41.7/ 40.0 years).

Table 1–3 give an account of the baseline (V2) and 8 weeks (V4) data in the 3 treatment groups. Assessments on the WHO-5 well-being scale (mean score: 9.4) and the Beck Depression Inventory (BDI, 16.0) indicate that subjects were, on average, impaired in their well-being but not to a degree requiring medical treatment. Mean salivary cortisol concentrations were within the normal range [31] at 14–21 nmol/L in the morning and an increase by 6.25 nmol/L 30 min after awakening (**Fig. 2**).

Efficacy

Mean values of the efficacy parameters at V2 and V4 are given in **Table 1–3**. Generally, most test parameters improved from visit to visit in all 3 treatment groups, with the exception of some cognitive parameters and physiological stress parameters. For example, the mean WHO-5 well-being score increased from 9.4 at V2 to 14.2 at V4, and the BDi-II depression score decreased from 16.0 to 8.0, both final values being in the reference range for normal populations.

For 2 parameters the 2-factorial ANOVA revealed significant interaction effects indicating a treatment effect: MFI-20 subscale "mental fatigue" improved more in group COM than in groups SMT and ES at V3, the difference still being significant for group COM vs. group ES at V4 (**Table 2**, **Fig. 3;** 2-factorial ANOVA: interaction group × visit $p=0.015$; 1-factorial ANOVA: group $p=0.038$; no gender effect). The MBDF subscale "calmness-restlessness" revealed superiority of combination therapy over ES at V3 and V4 (**Table 3**; 2-factorial ANOVA: interaction group × visit $p=0.032$; 1-factorial ANOVA: group $p=0.038$; no gender effect). Superiority of combination therapy over ES was also supported by a trend in the WHO-5 well-being scale (2-factorial ANOVA: interaction group × visit $p=0.087$; 1-factorial ANOVA: group $p=0.051$).

Table 1 Results of neuropsychological tests and self-assessment scales for cognitive parameters.

Cognitive performance	Parameter	Group	Baseline		8 weeks		
			Mean	±SD	Mean	±SD	Mean change
visual: path in town map	immediate recall	1: SMT	19.4	5.7	23.2	4.6	3.8
		2: COM	22.5	5.4	25.0	5.2	2.5
		3: ES	19.9	6.5	24.8	4.9	4.9
	delayed recall, loss of retain [%]	1: SMT	1.4	24.9	−3.4	15.1	−4.8
		2: COM	−6.1	29.0	−4.7	17.3	1.4
		3: ES	2.0	30.1	−7.4	15.7	−9.4
verbal: house construction data	immediate recall	1: SMT	11.9	4.4	15.7	4.8	3.8
		2: COM	13.2	4.7	17.7	3.8	4.5
		3: ES	11.7	5.2	16. 7	4.4	5.0
	delayed recall, loss of retain [%]	1: SMT	−1.4	30.7	−3.4	17.4	−2.0
		2: COM	8.5	37.0	−2.8	13.4	−11.3
		3: ES	12.9	69.2	−4.5	22.8	−17.4
working memory	correct answers	1: SMT	12.1	3.0	12.3	2.8	0.2
		2: COM	12.7	2.3	13.6	2.4	0.9
		3: ES	12.6	2.2	12.8	2.5	0.2
	reaction time [ms]	1: SMT	657.1	174.8	630.9	183.1	−26.2
		2: COM	658.1	191.4	625.3	141.5	−32.8
		3: ES	649.9	162.9	593.7	155.6	−56.2
divided attention	correct answers	1: SMT	31.5	1.1	31.4	1.6	−0.1
		2: COM	31.2	2.8	31.9	1.7	0.7
		3: ES	30.7	3.1	30.9	3.5	0.2
	reaction time audit. [ms]	1: SMT	612.4	105.2	601.4	91.3	−11.0
		2: COM	621.3	98.5	614.9	91.7	−6.4
		3: ES	615.0	100.6	590.9	103.7	−24.1
	reaction time visual [ms]	1: SMT	813.7	119.7	787.9	86.7	−25.8
		2: COM	819.3	185.1	764.6	85.3	−54.7
		3: ES	785.5	126.7	770.2	191.9	−15.3
go/NoGo	correct answers	1: SMT	23.9	0.4	23.9	0.4	0.0
		2: COM	23.9	0.4	24.0	0.2	0.1
		3: ES	23.7	1.4	23.9	0.2	0.2
	reaction time [ms]	1: SMT	580.5	77.2	579.3	82.9	−1.2
		2: COM	561.9	67.3	569.1	78.8	7.2
		3: ES	573.2	89.1	576.7	71.9	3.5
incompatibilty	incompatible/compatible errors	1: SMT	1.49	1.07	0.17	0.29	−1.3
		2: COM	0.00	0.00	1.16	0.00	1.2
		3: ES	1.33	0.94	0.00	0.00	−1.3
	interaction visual field/ hand	1: SMT	9.5	10.3	9.7	11.1	0.2
		2: COM	11.4	13.7	11.8	11.2	0.4
		3: ES	11.6	12.5	10.4	11.8	−1.2
	median search time [ms]	1: SMT	540.9	83.0	521.7	89.2	−19.2
		2: COM	532.0	81.8	522.4	90.2	−9.6
		3: ES	548.1	154.7	507.4	94.6	−40.7
visual scanning	missing critical symbols	1: SMT	7.80	6.92	6.10	5.03	−1.7
		2: COM	6.45	4.76	4.00	3.97	−2.5
		3: ES	7.94	8.30	4.69	5.16	−3.3
	search time for non-critical symbols [ms]	1: SMT	4727	1474	4037	1145	−690
		2: COM	5171	2258	4309	1751	−862
		3: ES	5080	1550	4382	1328	−698
KIA: Concentration in everyday life		1: SMT	3.21	0.42	2.91	0.45	−0.3
		2: COM	3.16	0.47	2.84	0.48	−0.3
		3: ES	3.05	0.38	2.82	0.40	−0.2

SMT: Stress Management Training; COM: combined treatment SMT + ES; ES: Eleutherococcus senticosus
No significant intergroup differences found

Satisfaction with therapy was highest in the combination group COM with a rating of 1.84 ± 1.05 on a Likert-scale from 1 to 5. The SMT group receiving training only followed with 1.92 ± 0.87, ES was ranked lowest with 2.41 ± 1.23. Differences were significant for COM vs. ES ($p = 0.02$) and SMT vs. ES ($p = 0.037$). Percentage of participants in groups SMT/COM/ES willing to continue treatment after study termination were 83.9 %/ 78 %/ 62.5 %.

Cortisol awakening response, i.e., the absolute increase within 30 min after awakening, significantly changed from visit 2 over visit 3 to visit 4 without group differences (**Fig. 2**; 2-factorial ANOVA, factor group $p = 0.24$; factor visit $p = 0.047$).

Table 2 Results of (self)-assessment scales relating to stress, fatigue and exhaustion.

Test, Subtest	Parameter	Group	baseline		8 weeks		
Feeling stressed			**Mean**	**±SD**	**Mean**	**±SD**	**Mean change**
TICS: Trier Inventory for chronic stress determination	work overload	1: SMT	64.2	9.9	55.2	9.6	−9.0
		2: COM	62.5	10.3	53.9	9.1	−8.6
		3: ES	64.6	10.3	57.6	9.5	−7.0
	social overload	1: SMT	59.8	11.6	53.5	8.7	−6.3
		2: COM	57.9	12.2	52.3	10.7	−5.6
		3: ES	59.0	14.5	53.4	13.3	−5.6
	pressure to perform	1: SMT	58.8	7.3	54.1	7.2	−4.7
		2: COM	58.8	9.7	52.0	8.2	−6.8
		3: ES	56.5	10.5	53.6	7.7	−2.9
	work discontent	1: SMT	62.1	9.2	57.2	9.8	−4.9
		2: COM	60.5	8.5	54.9	10.6	−5.6
		3: ES	61.9	8.4	56.5	9.7	−5.4
	excessive demands from work	1: SMT	64.1	7.6	57.5	9.2	−6.6
		2: COM	64.8	9.1	56.5	10.8	−8.3
		3: ES	64.1	9.1	59.2	8.6	−4.9
	lack of social recognition	1: SMT	62.3	8.1	57.7	8.2	−4.6
		2: COM	62.8	8.4	54.8	10.0	−8.0
		3: ES	60.9	9.5	56.3	9.5	−4.6
	social tensions	1: SMT	56.3	11.0	51.1	11.7	−5.2
		2: COM	61.5	10.3	53.8	11.2	−7.7
		3: ES	60.0	9.8	54.7	10.1	−5.3
	social isolation	1: SMT	56.6	9.0	52.1	11.2	−4.5
		2: COM	57.3	10.0	51.7	10.1	−5.6
		3: ES	59.3	11.7	53.4	9.7	−5.9
	chronic worrying	1: SMT	58.2	10.0	51.0	9.5	−7.2
		2: COM	59.2	10.5	51.8	10.3	−7.4
		3: ES	60.0	7.6	53.4	9.1	−6.6
SDS: Sheehan Disability Scale	global functional impairment	1: SMT	16.7	6.2	10.5	5.8	−6.2
		2: COM	16.8	6.2	9.3	5.8	−7.5
		3: ES	18.4	5.2	12.4	7.0	−6.0
	days unproductive	1: SMT	3.1	2.2	1.8	2.7	−1.3
		2: COM	3.5	2.6	1.3	1.9	−2.2
		3: ES	3.6	2.4	1.5	1.8	−2.1
	days lost	1: SMT	0.5	1.4	0.5	1.7	0.0
		2: COM	1.0	1.5	0.3	0.7	−0.7
		3: ES	1.0	1.9	0.3	0.7	−0.7
Fatigue, exhaustion							
MFI-20: Multi-dimensional Fatigue Inventory	general Fatigue	1: SMT	15.0	4.2	11.5	3.6	−3.5
		2: COM	14.3	3.8	10.7	4.0	−3.6
		3: ES	15.2	3.2	12.0	3.7	−3.2
	physical fatigue	1: SMT	12.7	3.7	10.0	3.6	−2.7
		2: COM	12.7	3.6	9.6	3.2	−3.1
		3: ES	14.1	2.8	11.0	3.4	−3.1
	mental fatigue	1: SMT	13.8	3.9	10.7	3.5	−3.1
		2: COM	14.2	3.0	* **9.7**	3.0	−4.5
		3: ES	13.7	2.7	* **11.0**	3.4	−2.7
	reduced activity	1: SMT	11.8	3.6	9.5	3.5	−2.3
		2: COM	12.0	3.9	9.9	2.9	−2.1
		3: ES	12.4	2.8	10.3	3.3	−2.1
	reduced motivation	1: SMT	11.2	3.3	9.1	2.7	−2.1
		2: COM	11.2	3.7	8.8	2.9	−2.4
		3: ES	12.0	2.5	9.9	2.9	−2.1
	total score mFI-20	1: SMT	64.4	14.3	50.5	14.1	−13.9
		2: COM	64.5	14.6	48.6	13.0	−15.9
		3: ES	67.4	9.2	54.2	14.1	−13.2
ASS-SYM:	exhaustion	1: SMT	16.6	4.0	10.7	5.0	−5.9
		2: COM	15.9	3.6	9.7	4.3	−6.2
		3: ES	16.7	3.1	12.2	4.2	−4.5

SMT: Stress Management Training; COM: combined treatment SMT + ES; ES: Eleutherococcus senticosus

Asterisk: group difference $p < 0.05$. Bold numbers indicate significant ($p < 0.05$) interaction in the 2-factorial ANOVA, i. e., a treatment effect

Table 3 Results of assessment scales and physiological stress parameters.

Test, Subtest	Parameter	Group	Baseline		8 weeks		
Alertness, restlessness, mood			Mean	± SD	Mean	± SD	Mean change
MDMQ: Multi-dimensional mood state questionnaire	good-bad mood	1: SMT	27.6	6.2	31.1	6.0	3.5
		2: COM	25.4	5.6	31.7	5.7	6.3
		3: ES	25.0	4.7	29.6	6.4	4.6
	alertness-fatigue	1: SMT	21.1	7.7	25.6	7.9	4.5
		2: COM	23.1	7.3	27.3	8.2	4.2
		3: ES	20.9	6.4	25.5	7.6	4.6
	calmness-restlessness	1: SMT	24.0	6.1	29.0	6.0	5.0
		2: COM	21.9	6.5	** **31.0**	5.2	9.1
		3: ES	21.5	6.1	** **27.4**	7.0	5.9
ASS-SYM:	tension	1: SMT	11.8	4.7	7.4	5.2	−4.4
		2: COM	12.3	3.9	7.5	3.9	−4.8
		3: ES	12.8	4.0	8.9	4.6	−3.9
	self-determination	1: SMT	10.4	4.8	6.1	5.0	−4.3
		2: COM	10.6	4.4	6.3	4.4	−4.3
		3: ES	10.3	4.4	6.8	4.2	−3.5
BDI-II: Beck depression inventory		1: SMT	14.5	8.7	6.6	6.2	−7.9
		2: COM	17.0	8.6	7.1	5.7	−9.9
		3: ES	16.4	6.9	9.9	7. 6	−6.5
WHO-5: Well-Being Index		1: SMT	* 10.5	5.0	14.6	4.5	4.1
		2: COM	9.4	4.4	** 15.9	4.4	6.5
		3: ES	* 8.4	4.3	** 12.5	5.8	4.1
LSEQ: Leeds Sleep Evaluation Questionnaire	getting to sleep	1: SMT	46.8	16.5	44.4	18.1	−2.4
		2: COM	47.9	14.5	40.9	16.4	−7.0
		3: ES	49.7	19.0	45.7	16.6	−4.0
	quality of sleep	1: SMT	57.9	21.7	45.4	23.6	−12.5
		2: COM	53.2	21.4	41.8	22.6	−11.4
		3: ES	57.4	21.9	49.3	18.8	−8.1
	awake following sleep	1: SMT	55.7	22.1	44.2	21.7	−11.5
		2: COM	45.8	18.3	41.0	19.0	−4.8
		3: ES	51.1	18.9	43.5	17.3	−7.6
	behaviour following wakening	1: SMT	60.4	15.5	46.9	20.5	−13.5
		2: COM	56.6	18.2	44.6	22.1	−12.0
		3: ES	60.7	13.8	47.4	17.9	−13.3
ASS-SYM:	dysregulation	1: SMT	7.5	4.7	4.3	4.3	−3.2
		2: COM	7.7	4.6	4.3	3.5	−3.4
		3: ES	8.3	4.4	4.9	3.2	−3.4
	burden of pain	1: SMT	8.6	4.7	5.0	4.0	−3.6
		2: COM	8.1	5.1	5.1	3.9	−3.0
		3: ES	7.9	3.8	5.2	3.1	−2.7
FFKA: Freiburg Questionnaire on Physical Activity		1: SMT	31.4	46.4	39.8	30.2	8.4
		2: COM	33.6	46.9	40.2	30.6	6.6
		3: ES	23.9	23.1	42.8	57.6	18.9
Physiological stress parameters							
Heart rate variabil.	mean square succ. interval diff.	1: SMT	64.9	129.4	108.0	150.9	43.1
		2: COM	40.5	103.5	101.2	170.3	60.7
		3: ES	37.9	92.4	93.4	140.2	55.5
Electrodermal (e.d.) activity	dermal conductability [µS]	1: SMT	12.1	5.4	10.1	5.2	−2.0
		2: COM	12.1	4.4	8.9	4.6	−3.2
		3: ES	14.0	7.4	11.3	7.0	−2.7
	number of e.d. responses [/ min]	1: SMT	47.4	17.8	39.9	18.5	−7.5
		2: COM	48.8	16.3	39.7	18.0	−9.1
		3: ES	47.1	15.8	38.7	18.5	−8.4
	accumulated amplitude [µS]	1: SMT	20.2	14.9	17.1	12.7	−3.1
		2: COM	18.7	12.7	17.3	14.3	−1.4
		3: ES	21.3	16.2	19.4	17.9	−1.9
Salivary cortisol: awakening profile	awakening response[1] [nmol/l]	1: SMT	6.1	6.7	5.7	6.3	−0.4
		2: COM	5.0	7.9	5.1	7.6	0.1
		3: ES	7.5	7.1	6.6	7.2	−0.9
	sum[2] [nmol/l]	1: SMT	768	236	778	311	10
		2: COM	853	310	800	272	−53
		3: ES	878	256	846	322	−32

Table 3 Continued.

Test, Subtest	Parameter	Group	Baseline		8 weeks		
Physiological stress parameters			Mean	± SD	Mean	± SD	Mean change
Salivary cortisol: diurnal profile	diurnal time profile[3] [nmol/l]	1: SMT	−4.1	5.4	−4.6	5.8	−0.5
		2: COM	−5.9	6.5	−5.3	4.9	0.6
		3: ES	−4.8	5.4	−4.0	5.9	0.8
	diurnal sum[4] [nmol/l]	1: SMT	70.1	24.8	69.7	24.4	−0.4
		2: COM	74.4	32.2	74.6	27.0	0.2
		3: ES	78.5	38.2	77.1	40.1	−1.4

SMT: Stress Management Training; COM: combined treatment SMT + ES; ES: Eleutherococcus senticosus

Asterisk: group differences significant at * $p<0.05$; ** $p<0.01$ level. Bold numbers indicate significant ($p<0.05$) interaction in the 2-factorial ANOVA, i. e., a treatment effect

[1]difference between measures taken 30 min after awakening and at awakening [2] sum of measures at awakening, + 30 min, + 45 min [3] difference between measures taken at 3 p.m. and 9 a.m. [4] sum of measures at 9 a.m., 3 p.m., and 9 p.m

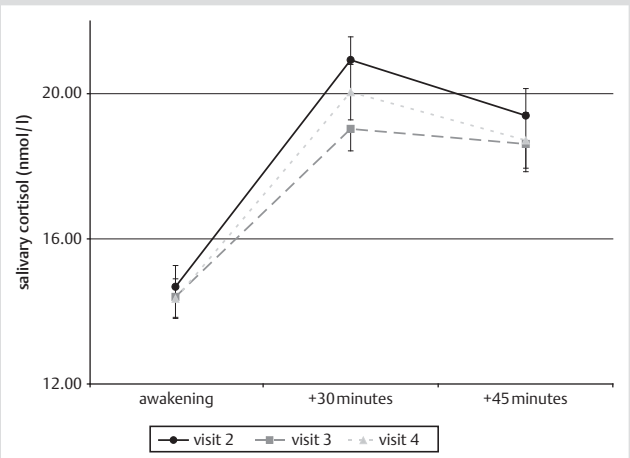

Fig. 2 Cortisol awakening response in the total sample (n = 128). Absolute cortisol increase within 30 min significantly changed from visit 2 (baseline) over visit 3 (week 2) to visit 4 (week 8; two-factorial ANOVA, factor visit p = 0.047; mean ± SE).

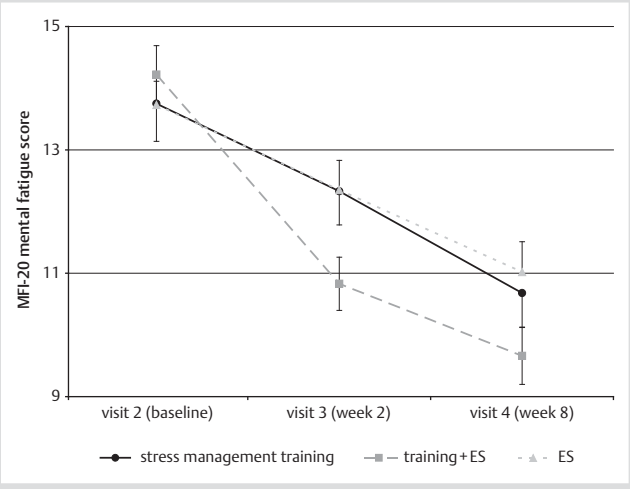

Fig. 3 Time course of MFI-20 subscale "mental fatigue" from visit 2 to visit 4. Differences between combination treatment (COM) and training as well as COM and ES were significant at visit 3, and between COM and ES at visit 4 (all $p<0.05$, t-test). Lower score means less fatigue (mean ± SE).

Safety

No severe or serious adverse events or clinically relevant laboratory parameter changes occurred in this trial. From V2 to V4, 8 adverse events were recorded in group SMT, 18 adverse events in group COM and 27 adverse events in group ES. For none of the adverse events a likely causal relation to treatment was established. Most common adverse events in group COM were common cold and influenza (2 each), in group ES headache (4), herpes labialis (3) and common cold (2).

Discussion

General well-being, stress-related complaints and cognitive performance improved in most of the parameters tested in this trial, and some of them to a considerable extent. The study medication and the training programs were well tolerated and safe. Stress management training was associated with high treatment satisfaction and about 80 % willingness to continue behavioural strategies acquired from the training.

The statistical design of the study was adequate to demonstrate significant changes from visit to visit even when these were smaller than the variances. However, there were only a few parameters demonstrating statistically significant treatment differences. Wherever differences exist, they suggest that combination therapy may be more effective than taking ES alone. In none of the evaluated parameters was the addition of taking ES to stress management training superior to training alone. The fact that we detected statistically significant treatment differences confirms the assay sensitivity of our study, i. e., the ability to detect treatment effects. In our exploratory trial, we did not correct level of significance for multiple testing. The fact that all observed treatment differences favoured one of 3 treatment groups suggests that the findings reflect a real treatment effect and not chance variations.

When evaluating subjective and psychophysical parameters by repeated testing in a clinical trial context in subjects with stress-related symptoms, outcomes will be affected by important unspecific effects [33]. Therefore the reported improvements over time should be interpreted as a combination of pharmacological treatment effects, subject and investigator expectations, regression to the mean, spontaneous improvement, a Hawthorne effect, training effects in case of neuropsychological tests, and adaptation to the test situation for physiological parameters. Such unspecific effects, often subsumed into the term "placebo effect", can be an important, sometimes the most important, source of clinical benefit. As we were interested in estimating the clinical benefit of the treatment strategy "adding regular intake of ES" in this patient group, not in measuring pure pharmacological effect size, we deliberately did not conduct a

placebo-controlled trial. Because the combination of ES plus SMT was not better than SMT alone in any parameter, we did not even observe a placebo effect, i.e., the psychological benefit and expectations associated with the regular intake of a promising drug. Therefore, lack of a placebo control in our trial does not impact our conclusion.

In a context, where several treatment strategies are commonly used but combinations have not been systematically tested, our exploratory 3-arm trial design without placebo control proved to be efficient to arrive at a go/nogo decision for the next step in clinical research: a large placebo-controlled confirmatory trial. Certainly, the main limitation of our trial design is that it does not allow us to draw conclusions on the absolute size of specific effects of ES or SMT therapy. These questions have to be addressed in a standard phase III trial design [32].

Our study population was bothered by considerable amounts of occupational and social chronic stress as evidenced by baseline mean TICS values 1–2 standard deviations above population averages. Symptoms were severe enough to make the participants seek professional help. Nevertheless, normal average baseline salivary cortisol levels, diurnal profiles and awakening responses indicate that subjects were not suffering from chronic stress severe enough to affect the HPA-axis to an extent resulting in abnormal mean values. Our study was sufficiently powered to detect a small transient attenuation of the cortisol awakening response without group differences. We interpret this as a Hawthorne effect, i.e., the benefit and relief from participating in a clinical trial. Since "the effect of an adaptogen is as pronounced as the deeper are pathological changes in the organism" [7] and modulation of the HPA-axis has been postulated as a mode of action, the potency of the study medication may not have been fully exploited. While we could not detect effects in subjects seeking support for chronic stress typically associated with western urban lifestyle, we cannot exclude that adding ES to non-pharmacological interventions has measurable benefits that have been reported from earlier trials in extreme stressful situations, such as military long-term-flights, submarine crew members, Olympic games, or space flights [8].

ES extraction parameters and pharmaceutical quality, dosing, mode of administration and treatment duration of the medicinal product were in agreement with monographs and tradition. The assessment report of the EMA Herbal Medicinal Products Committee (HMPC) in 2008 concluded that "none of the studies would be sufficient to substantiate efficacy of ES preparations in a clearly defined clinical condition, although, in total, the data available are sufficient to justify further research into the concept of adaptogens" [8]. Some more recent reports from controlled studies were in line with older findings that ES may increase endurance capacity [34], reduce cardiovascular stress response to a test situation [35] and transiently improve quality of life in elderly patients with cardiovascular diseases [36], but methodological shortcomings criticized by the HMPC also apply to these investigations, especially due to the low numbers of subjects included. A larger trial on 96 volunteers suffering from chronic fatigue did not find superiority of ES over placebo [37]. Likewise, we did not observe any additional effects when adding ES to SMT.

Yarnell et al. [38] recommend ES "for patients suffering from physical stress from work or exercise" and "athletes searching for a safe alternative to hormones" rather than for subjects suffering from mental stress, where they prefer *Rhodiola rosea*. A considerable number of clinical studies gave promising results for preparations from this plant for a wide range of applications including fatigue, cognitive functioning, depression and anxiety [39,40]. A systematic review of randomized clinical trials concluded that *Rhodiola rosea* may have beneficial effects on physical performance, mental performance, and certain mental health conditions [41]. A recent open trial with the standardized *Rhodiola rosea* dry extract WS® 1375 in subjects with life stress symptoms found clinically relevant improvements of stress symptoms, disability, and functional impairment [42]. This finding is currently re-evaluated in burn-out patients (EUCTR2010–022686–10-AT) and a controlled trial of the effects on physiological and psychological responses to psychological stress assessed under laboratory conditions and in everyday life has recently been completed in the UK (EUCTR2009-017806-36-GB). Although ginseng, Siberian ginseng, roseroot and Chinese magnolia vine have been classified as "adaptogens" based on tradition, theory, and animal experiments, clinical evidence does not support this concept. Plant adaptogens have to be evaluated clinically on a case-by-case basis and should not be seen as a homogenous class of compounds.

In sum the current study failed to find beneficial effects of adding regular intake of Siberian ginseng to stress management training on subjective well-being measures, cognitive tests as well as physiological stress markers in subjects experiencing high stress levels and seeking help for impaired working performance, concentration capability, fatigue and weakness.

Conflict of Interest

K. Schaffler was the LKP of the multi-center study and has no conflict of interest.

Oliver T. Wolf has worked as a consultant for Dr. Willmar Schwabe GmbH & Co. KG.

Martin Burkart is employee of Dr. Willmar Schwabe GmbH & Co. KG, the sponsor of the trial and marketing authorisation holder of WS® 1070.

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