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Double-blind, placebo-controlled, randomised study of single dose effects of ADAPT-232 on cognitive functions

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ABSTRACT

The aim of this study was to assess the effect of a single dose of ADAPT-232 (a standardised fixed combination of *Rhodiola rosea* L., *Schisandra chinensis* (Turcz.) Baill., and *Eleutherococcus senticosus* Maxim) extracts on mental performance, such as attention, speed and accuracy, in tired individuals performing stressful cognitive tasks.

The pilot study (phase IIa) clinical trial took the form of a double-blind, placebo-controlled, randomised, with two parallel groups. Forty healthy females aged between 20-68 years, who claimed to have felt stressed over a long period of time due to living under psychologically stressful conditions were selected to participate in the pilot study. In addition, a Stroop Colour-Word test (Stroop CW) was used to exhaust/prepare the volunteers prior to the d2 test used for assessment of cognitive function of patients.

The participants were randomised into two groups, one (*n=20*) of which received a single tablet of ADAPT-232 (270 mg), while a second (*n=20*) received a single tablet of placebo.

The effects of the extract were measured prior to treatment and two hours after treatment using the d2 Test of Attention (d2). The results of the d2 test showed a significant difference ($p < 0.05$) in attention, speed, and accuracy (TN-E scores) between the two treatment groups. The subjects in the ADAPT-232 group quickly (two hours after verum was taken) gained improved attention and increased speed and accuracy during stressful cognitive tasks, in comparison to placebo. There was also a tendency of ADAPT-232 to reduce percentage of errors, which means better accuracy, quality of the work, and degree of care in the volunteers under stressful conditions. No serious side effects were reported, although a few minor adverse events, such as sleepiness and cold extremities, were observed in both treatment groups.

Introduction

A group of herbal preparations known collectively as adaptogens (Brekhman and Dardymov, 1969; Panossian et al., 1999; Panossian, 2004) can increase tolerance to mental exhaustion and may enhance attention in cases of decreased performance, such as in fatigue and in the sensation of weakness (Olsson et al., 2009; Panossian and Wikman, 2009; Panossian and Wikman, 2010). The beneficial effects of multi-dose administration of adaptogens are mainly associated with the hypothalamic-pituitary-adrenal axis, a part of the stress-system that is believed to play a primary role in the reactions of the body to repeated stress and adaptation (Panossian et al., 1999; Olsson et al., 2009; Panossian et al., 2007; Panossian and Wikman, 2008; Panossian and Wikman, 2010). A single dose application of adaptogens is important in situations, which requires a rapid response to tension or to a stressful situation (Panossian and Wagner, 2005). Additionally, a single administration of these adaptogens increases mental performance and physical working capacity in humans (Panossian and Wagner, 2005).

The use of herbal preparations derived from *Rhodiola rosea* L, *Schizandra chinensis* (Turcz.) Baill. and *Eleutherococcus senticosus* Maxim. is not generally associated with deleterious side effects. In contrast, traditional stimulants may cause addiction, tolerance and abuse, and give rise to negative effects on sleep structure, thus cause rebound hypersomnolence or "come down" effects.

ADAPT-232 is a standardised fixed combination of extracts of *R. rosea*, *S. chinensis* and *E. senticosus*. The aim of the present double-blind, parallel-group, randomised, pilot (phase IIa) study was to evaluate the effect of a single dose of ADAPT-232 on

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mental performance, such as attention, speed, and accuracy, on tired subjects performing stressful cognitive tasks.

Subjects and Methods

The study protocols were reviewed and approved by the Ethics Committee of the Armenian Drug and Medical Technology Agency of the Ministry of Health of the Republic of Armenia. The pilot study involved 40 patients and was carried out at the Department of Clinical Pharmacology of the National Institute of Health (Yerevan, Armenia) between January and February 2008.

Study population

The study population included healthy female volunteers (nurses, doctors and teachers), which were recruited from a polyclinic, a school and a hospital close to the Department of Clinical Pharmacology. The included individuals, aged between 20-68 years, had experienced stress over a long period of time due to living under psychologically stressful conditions.

Pregnant or breast-feeding subjects; individuals with identified medical conditions (e.g. HIV, cancer or cardiovascular, joint, liver, kidney or psychiatric diseases); those diagnosed with psychiatric problems; those presenting allergic reactions to herbal products; those who had used adaptogens within the previous two months or corticosteroids within the previous 6 months; those misusing tranquillisers, pain killing drugs or narcotics; those suffering from caffeine withdrawal syndrome or were heavy coffee drinkers; and those subjects who were deemed to be unwilling to cooperate or unable to participate in the study were excluded.

The strict requirement to avoid coffee during the complete period of the trial and to abstain from alcohol and caffeine for a minimum of one day prior to the testing session on the morning of the first day of the trial and throughout the following three days was carefully explained to all volunteers. The selected participants, who also accepted the trial protocol, were included in the double-blind comparative study. Written informed consent was obtained from each participant in accordance with the revised declaration of Helsinki (World Medical Association Declaration of Helsinki, 2000).

Study drugs

The study drugs were manufactured according to Good Manufacturing Practice (GMP) by the Swedish Herbal Institute (Gothenburg, Sweden) and presented in the form of tablets. The ADAPT-232 (batch 1121) tablets comprised a fixed combination of dried extracts from roots of *R. rosea* (drug extract ratio 2.8:1; extraction solvent 70% ethanol), berries of *S. chinensis* (drug extract ratio 1.4:1; extraction solvent 95% ethanol) and roots of *E. senticosus* (drug extract ratio 10.5:1; extraction solvent 70% ethanol), and had been standardised with respect to rhodioloside (0.32%), rosavin, (0.5%), tyrosol (0.05%) schizandrin (0.37%), γ-schizandrin (0.24%) and eleutherosides B and E (0.15%). The verum was presented as a single 420 mg tablet, which contains 270 mg of ADAPT-232.

The amounts of the active ingredients were determined by analytical RP-HPLC using an acetonitrile-water gradient system as mobile phase. The peaks were detected by UV-PAD (Fig. 1) and the analytes were quantified at 221 nm (rhodioloside and tyrosol), 252 nm (rosavin), 220 nm (eleutheroside B), and 210 nm (eleutheroside E, schizandrin and γ-schizandrin). All the analytical methods were validated for selectivity, peak purity, precision (RSD < 5%) and accuracy in the range 50 - 150% of the target amounts of analytes in accordance with International Conference on Harmonisation (ICH) guidelines (International Conference on Harmonization, 1995) using Effi Validation 3 software (version 1.03) for testing and calibration laboratories subject to EN ISO/IEC 17 025:2001 (International Organisation for Standardisation, 2001).

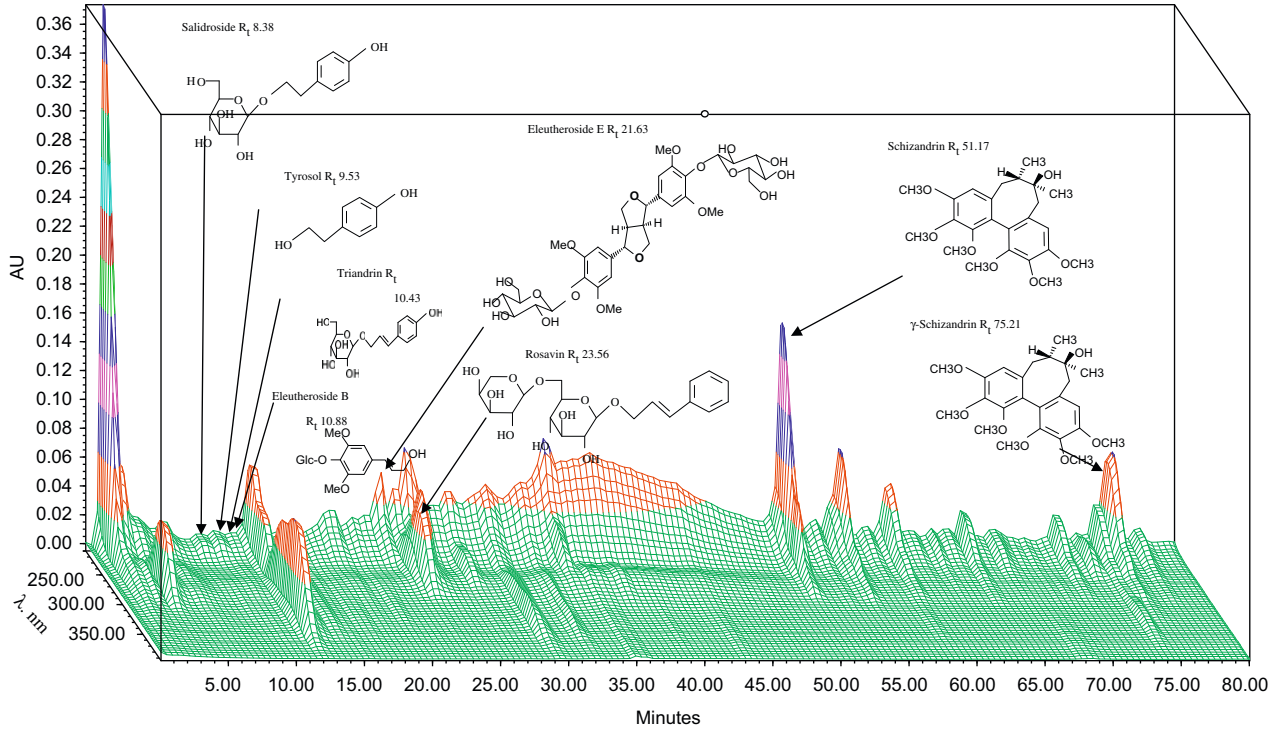

Fig. 1. HPLC fingerprint of ADAPT-232. R_t is the retention time (min).