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Comparative study of Rhodiola preparations on behavioral despair of rats

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Abstract

The antidepressant-like activity of an extract of the roots of *Rhodiola rosea* (RR), its combination with piperine containing extract (RPE), pure substances isolated from *Rhodiola*, such as rhodioloside, rosavin, rosin, rosarin, tyrosol, cinnamic alcohol, cinnamaldehyde and cinnamic acid has been assessed in laboratory animals through application of the Porsolt behavioural despair assay. RR increased the swimming time of rats in a dose dependent manner (ED50 = 7 mg/kg) and, when administered at 20 mg/kg, exhibited a stronger anti-depressant type effect than either imipramine (at 30 mg/kg) or an extract of *Hypericum perforatum* (at 20 mg/kg). Rhodioloside, and tyrosol were identified as active principles of the extract, whereas rosavin, rosarin, rosin, cinnamic alcohol, cinnamaldehyde, cinnamic acid were inactive. A fixed combination of rhodioloside, rosavin, rosarin and rosin was more active than any of the individual components alone, indicating a synergistic effect of the ingredients in RR extract. Piperine in combination with Rhodiola (RPE) distorts pharmacological effect of Rhodiola most probably due to changes of pharmacokinetic profile of rhodioloside and rosavin. RPE cannot provide predictable therapeutic effect due to herb–herb interaction. Moreover, concomitant treatment of RPE with other drugs should also be excluded due to drug–piperine interaction.

Keywords: *Rhodiola rosea*; Rhodioloside; Rosavin; Piperine; Anti-depressant; Drug–herb interaction

Introduction

Rhodiola rosea L. is a valuable medicinal plant known mainly as an adaptogen increasing resistance to the harmful effects of various stressors (Boon-Niermeijer et al., 2000; Darbinyan et al., 2000; Panossian et al., 2007; Perfumi and Mattioli, 2007; Saratikov and Krasnov, 2004; Spasov et al., 2000; Shevtsov et al., 2003; Sokolov et al., 1985). In the course of our systematic research on chemistry and pharmacology of adaptogens (Boon-Niermeijer et al., 2000; Darbinyan et al., 2000; Narimanian et al., 2005; Panossian and Wikman, 2005; Panossian and Wagner, 2005; Panossian et al., 1999a, b, 2007; Spasov et al., 2000; Shevtsov et al., 2003) we decided to evaluate a possible anti-depressant effect of *Rhodiola rosea* extract. Clinical trials carried out in 1986 and 1987 by Brichenko and co-workers in Russia (Brichenko et al., 1986; Brichenko and Skorokhodova, 1987) demonstrated that when *R. rosea* is administered together with tricyclic anti-depressants there is a marked reduction in the side effects of the drugs and an additional positive effect on psychopathological symptoms in patients with psychogenic depression. The results of a recent pilot clinical trial of RR demonstrated the anti-depressive potency of the drug in patients with mild to moderate depression (Darbinyan et al., 2007).

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One of the objectives of the present study was to identify active principle of RR extract and possible synergistic effect of active constituents, using an appropriate animal system. A subproject was to study the combination of RR and a piperine containing extract. As piperine itself has shown antidepressant effect (Lee et al., 2005; Li et al., 2007) and also is known to favor the uptake of active substances (Atal et al., 1981) the hypothesis was to have an efficient fixed combination of *Rhodiola* and piperine containing extract. Porsolt et al. (1977a, b, 1978) proposed a test involving the assessment of behavioural despair in laboratory animals as a model for determining antidepressant activity. Rats and mice that are repeatedly forced to swim in a restricted space succumb to immobility as a characteristic behavioural outcome. This endpoint reflecting a state of despair is significantly changed by agents which have been shown to be therapeutically effective in human depression.

In the present study, we have been able to identify active compounds of Rhodiola which are active in Porsolt's behavioral despair test and demonstrate their synergistic action in experiments involving laboratory animals *in vivo*. We found also that the combination of piperine with Rhodiola distorts pharmacological effect of Rhodiola most probably due to changes of the pharmacokinetic profile of active ingredients.

Materials and methods

Details of the project were submitted to 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 principles of laboratory animal care, as delineated in EEC Directive 75/318 (1994), were followed throughout the study.

Study drugs

Extracts of roots of *Rhodiola rosea* L. containing 2.7% rhodioloside, 6.0% rosavin and 0.8% tyrosol ($DER_{genuine}$ 2.5–5.0:1. batches EX20404 and EX20465, HPLC fingerprint is on the Fig. 1) were supplied by the Swedish Herbal Institute (Gothenburg, Sweden). High purity reference standards of rosavin, rosarin, rosin, rhodioloside and tyrosol were kindly provided by G. Zapesochnaya (Vilar, Moscow, Russia). Cinnamic acid, cinnamaldehyde and cinnamic alcohol were from Sigma-Aldrich (St. Louis, MO, USA). The commercial product Jarsin 300® (batch 96021102) was purchased from Lichtwer Pharma (Berlin, Germany) and contained ca. 1% hyperforin, 0.1% hypericin and 0.1% pseudohypericin per dosage form. Apo-Amitriptyline® tablets were purchased from Apotex (Toronto, Canada) and contained 10 mg of amitriptyline per tablet (batch L D40Z0). Imipramine hydrochloride (Gedeon Richter, Budapest, Hungary: batch 63074098 containing 12.5 mg/ml) was diluted with water to a concentration of 6 mg/ml. Black Pepper (*Piper nigrum*) fruit was purchased from Alfred Galke GmbH (37534 Gittelde/Harz, Germany, total content of piperine analogs – 5%) and extracted with 50% ethanol. Fixed combination (RPE) of *Rhodiola rosea* (RR) and *Piper nigrum* extracts (PN) was prepared at Swedish Herbal Institute (the ratio

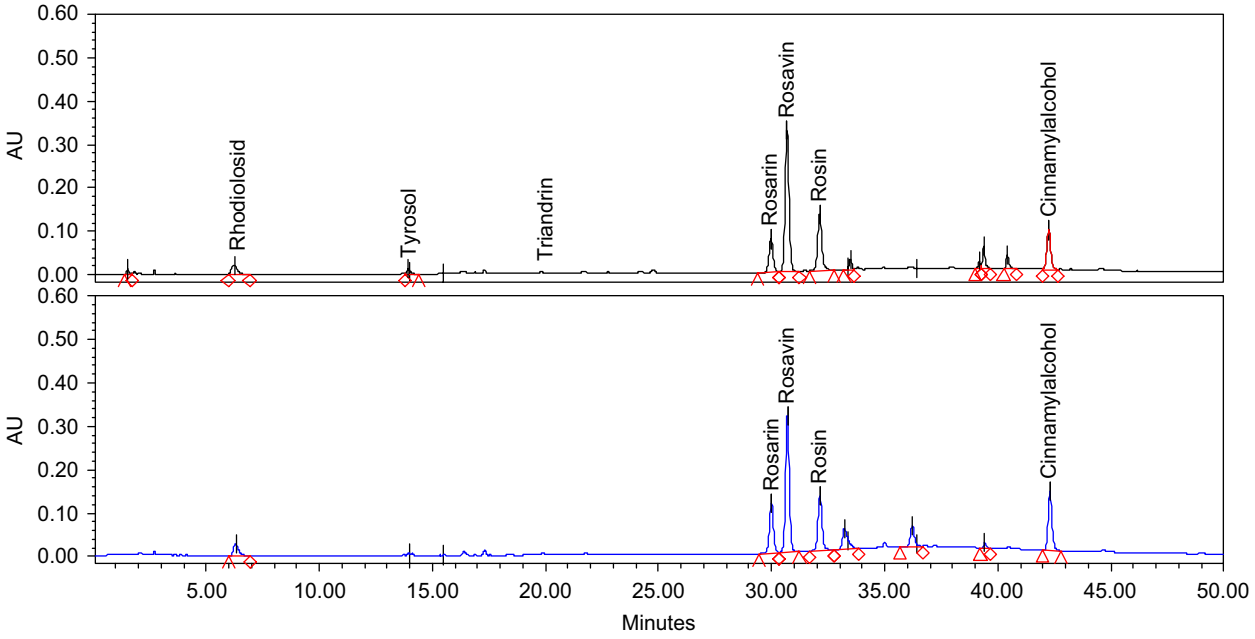

Fig. 1. HPLC fingerprint of two different batches of RR at 252 nm.