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Adaptogenic and Central Nervous System Effects of Single Doses of 3% Rosavin and 1% Salidroside *Rhodiola rosea* L. Extract in Mice

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***Rhodiola rosea* L., or 'golden root', is a popular plant in traditional medicine in Eastern Europe and Asia, with a reputation for improving depression, enhancing work performance, eliminating fatigue and treating symptoms of asthenia subsequent to intense physical and psychological stress. Due to these therapeutic properties, *R. rosea* is considered to be one of the most active adaptogenic drugs. To confirm and extend results obtained in the few preclinical and clinical studies available in English language journals, the purpose of the present study was to re-investigate the effects produced by a single oral administration of an *R. rosea* hydroalcohol extract (containing 3% rosavin and 1% salidroside) on the central nervous system in mice. The extract was tested on antidepressant, adaptogenic, anxiolytic, nociceptive and locomotor activities at doses of 10, 15 and 20 mg/kg, using predictive behavioural tests and animal models. The results show that this *R. rosea* extract significantly, but not dose-dependently, induced antidepressant-like, adaptogenic, anxiolytic-like and stimulating effects in mice. This study thus provides evidence of the efficacy of *R. rosea* extracts after a single administration, and confirms many preclinical and clinical studies indicating the adaptogenic and stimulating effects of such *R. rosea* extracts. Moreover, antidepressant-like and anxiolytic-like activities of *R. rosea* were shown in mice for the first time. Copyright © 2006 John Wiley & Sons, Ltd.**

Keywords: Rhodiola rosea; adaptogenic activity; CNS activities; swimming test; light-dark test; open-field test.

INTRODUCTION

Rhodiola rosea L. (Family *Crassulaceae*), the most important species of the genus Rhodiola, is a shrub that is widely distributed at high altitudes in the Artic and in mountainous regions throughout Europe and Asia, where it is also known as 'golden root' or 'artic root' (German *et al.*, 1999). This plant is very popular in traditional medicine, with a reputation for alleviating emotional, mental and physical disorders (German *et al.*, 1999; Spasov *et al.*, 2000; Shevtsov *et al.*, 2003; Saratikov and Krasnov, 2004; Panossian and Wagner, 2005).

R. rosea is used in traditional folk medicine to stimulate the nervous system, to decrease depression, to enhance work performance, longevity and resistance to high altitude sickness, and to treat fatigue and symptoms of asthenia subsequent to intense physical and psychological stress (Kelly, 2001; Brown *et al.*, 2002; Zhu *et al.*, 2003). Therefore, due to its ability to increase the resistance of an organism to environmental stress factors and to avoid damage from such factors, *R. rosea* has been defined as an 'adaptogen' (Wagner *et al.*, 1994; Panossian *et al.*, 1999; Panossian, 2003; Panossian and Wagner, 2005).

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Phytochemical investigations on the roots of *R. rosea* have resulted in the isolation of a range of biologically active substances, including organic acids, flavonoids, tannins and high amounts of phenolic compounds. In particular, these last include phenylpropane derivatives, such as the rosavins (rosavin, rosine, rosarin), which are specific components of *R. rosea*, and phenylethane derivatives, such as salidroside, which is present in all species of the *Rhodiola* genus and in a wide variety of species outside this genus (Kurkin and Zapesochnaya, 1986; Wang *et al.*, 1992; Yoshikawa *et al.*, 1996; Linh *et al.*, 2000). According to the revised 1989 Soviet Pharmacopeia (Brown *et al.*, 2002), extracts of *R. rosea* are standardized for both rosavins and salidroside.

Some preclinical and clinical studies of *R. rosea* extracts have provided evidence for a number of pharmacological activities, including adaptogenic, antistress, antihypoxic, antioxidant, anticancer, learning and memory enhancing and immune and sexual stimulating effects (Petkov *et al.*, 1986; Darbinyan *et al.*, 2000; Ming *et al.*, 2005; Panossian and Wagner, 2005). Rosavine, salidroside and additional phenolic compounds, including p-thyrosol and triandrin, are thought to be critical in the actions of this adaptogen and the central effects of this plant, while organic acid and flavonoids have been demonstrated to contribute to the antioxidant and anticancer activities of crude extracts of *R. rosea* (Furmanowa *et al.*, 1998; Ming *et al.*, 2005).

Although the adaptogenic and central nervous system activities of *R. rosea* have been studied extensively, preclinical investigations, in particular, are

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fragmentary and often not comparable due to the various extracts and different modalities of their administration (single or repeated); many are also not available in English language journals.

Therefore the purpose of the present study was to re-investigate the effects of acute administration of *R. rosea* L. on the central nervous system in mice, using different predictive behavioural tests and animal models. Since *R. rosea* extracts used in several preclinical and clinical studies have been standardized to a minimum of 3% rosavins and 0.8–1.0% salidroside (Darbinyan *et al*., 2000; Kelly, 2001; Brown *et al*., 2002; Abidov *et al*., 2003; Panossian and Wagner, 2005), a *R. rosea* L. hydroalcohol extract containing 3% rosavin and 1% salidroside was used.

MATERIALS AND METHODS

Animals. Male CD1 mice (20–25 g; Harlan SRC, Milan, Italy) were housed in groups of 7–10 in a room with a standard light/dark cycle (lights on: 07.00 to 19.00 h), and at constant temperature (20–22 °C) and humidity (45–55%). The mice were given free access to food pellets (4RF; Mucedola, Settimo Milanese, Italy) and tap water. The animals were handled once a day for 5 min during the first week after their arrival. All experiments were performed during the light period, and were conducted according to the European Community Council Directive for Care and Use of Laboratory Animals (86/609/EEC).

Drugs. A dry hydroalcohol extract from the roots of *Rhodiola rosea* L. was used (RHO; EPO S.r.l., Milan, Italy). The HPLC analysis report showed a content of 3% total rosavins, expressed as rosavin, and 1% salidroside. The ratio of rosavin and salidroside (3:1) is in line with published data (Abidov *et al*., 2003; Kurkin and Zapesochnaya, 1986). The extract was dissolved in 2% ethanol and diluted in tap water, and then administered acutely by intragastric (i.g.) administration, at doses of 10, 15 and 20 mg/kg, 1 h before experiments.

Antidepressant-like activity. To evaluate the antidepressant-like activity of RHO, the forced-swimming test was used, the best recognized pharmacological model for assessing antidepressant-like activity in rodents (Porsolt *et al*., 1977a,b; Borsini and Meli, 1988; Willner, 1990). The development of learned helplessness syndrome, when mice are placed in a cylinder filled with water that they cannot escape from, reflects the cessation of persistent escape-directed behaviour, as seen by increased periods of immobility (Lucki, 1997). The reduction in immobility is considered as a behavioural profile that is consistent with an antidepressant-like action (Cryan *et al*., 2002).

Briefly, the animals ($n = 40$) were randomly divided into four groups, each of which received i.g. administration of vehicle or RHO at 10, 15 and 20 mg/kg. One hour later, the mice were placed individually in a glass cylinder (20 cm in height, 14 cm in diameter) filled to a 10 cm depth with water (23 ± 1 °C). At this water depth, the mice could touch the bottom of the jar with their tail, but they could not support themselves with their hind limbs. Each mouse was given a 6 min swimming test, and the duration of immobility was noted during the final 4 min interval of the test, since the first 2 min were used to allow the animals to familiarize themselves with the surroundings. All the swim-test sessions were recorded by a video camera positioned directly above the cylinder. Two experienced observers, who were blind to the treatment conditions, scored the videotapes. An immobility period was regarded as the time spent by the mouse floating in the water without struggling and while making only the very slight movements that are necessary to keep its head above the water. Following these swimming sessions, the mice were towel dried and returned to their housing. Each animal was tested only once.

Adaptogenic activity: Swimming to exhaustion test. The ability of adaptogens to increase work capacity and physical performance has often been assessed using the swimming test in rodents, under different experimental conditions. Indeed, both adaptogens and antidepressants can increase the amount of time that an animal is able to keep swimming actively (Brekhman and Dardymov, 1968; Espinola *et al*., 1977; Banerjee and Izquierdo, 1982; Singh *et al*., 1988; Wagner *et al*., 1994; Dhuley, 2000; Abidov *et al*., 2003).

Briefly, the mice ($n = 32$) were randomly divided into four groups that received i.g. administration of vehicle or RHO at 10, 15 and 20 mg/kg. One hour later, the mice were individually placed in a glass cylinder (see above) where they were allowed 20 min for exhaustive swimming. The maximum duration of swimming was estimated on the basis of preliminary studies. The time spent swimming was noted during the final 18 min of the test, by two observers who were blind to the treatment conditions. Following the swimming sessions, the mice were towel dried and returned to their housing. Each animal was used only once.

Anxiolytic-like activity. A relevant test system to detect anxiety-related behaviour in mice is the light/dark exploration test, which uses the aversion of rodents for brightly lit large spaces (Crawley, 1981; Hascoet and Bourin, 1998; Hascoet *et al*., 2001; Bourin and Hascoet, 2003). The light-dark apparatus consisted of an open-topped rectangular Plexiglas box (45 × 30 × 30 cm; l × b × h) that was divided into a small (18 × 30 cm) area and a large (27 × 30 cm) area with an opening door (7.5 × 7.5 cm) located in the centre of the partition at floor level. The small compartment was painted black and stayed dark, whereas the large compartment was painted white and was brightly illuminated with a 60 W (400 lx) light source.

Briefly, the mice ($n = 32$) were randomly divided into four groups that received i.g. administration of vehicle or RHO at 10, 15 and 20 mg/kg. One hour later, each animal was placed at the centre of the illuminated compartment, facing one of the dark areas. The latency time for their first passage from the light compartment to the dark one, the number of entries into each compartment, the time spent in the illuminated area, and the number of times that the mouse reared on its hindpaws in the light space (rearing), were recorded for 5 min (Crawley and Goodwin, 1980).

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Locomotor and anxiolytic-like activities. The open-field test is a classical system that is routinely used to evaluate general locomotor activity and anxiety-related behaviour of animals (Ramos and Mormede, 1998; Carola *et al*., 2002; Prut and Belzung, 2003). This paradigm mimics the natural conflict in mice between their tendencies to explore a novel environment and to avoid an open area (Crawley, 1985; Asano, 1986). The open-field apparatus consisted of a square arena (43.2 × 43.2 cm) that was divided into a central and a peripheral zone (central zone coordinates: 3/3, 3/13, 13/3, 13/13) by an infrared photobeam (MED Associates Inc., USA, Vermont). The arena was lit by two red-light lamps (2 × 60 W) placed over its centre. One hour before the test, the mice (n = 36) were divided into four groups that received i.g. administration of vehicle or RHO at 10, 15 and 20 mg/kg. The test was initiated by placing a single mouse in the middle of the arena and letting it move freely for 5 min.

A number of conventional and ethological parameters (Walsh and Cummins, 1976; Choleris *et al*., 2001) were collected during the session. The horizontal activity (i.e. distance travelled, ambulation time, resting time) and the vertical activity (i.e. rearing) in the central and peripheral zone were recorded automatically (software settings: box size: 4; ambulatory trigger: 2; resting delay: 1500 ms) (Karl *et al*., 2006). The time spent in the central area, and the ambulation time and vertical activity in this zone, are indicators of the emotional reactivity of the mouse, as the central area of a novel environment is anxiogenic and aversive (Denenberg, 1969; Carola *et al*., 2002; Meyer *et al*., 2006). Therefore, these were taken as measures of anxiety. Moreover, the number of fecal boli passed during the test was positively correlated with emotion (Lister, 1990), and negatively correlated with locomotor activity (Ossenkopp and Mazmanian, 1985). The arena was carefully cleaned with alcohol and rinsed with water after each test, to removed environmental odours.

Nociceptive assay. The study also investigated the ability of RHO to modulate nociception using the classic tail-flick test (Langerman *et al*., 1995; Gardmark *et al*., 1998; Malmberg and Bannon, 1999). Radiant heat was focused on a blackened spot 1–2 cm from the tip of the mouse tail and the latency to a tail flick was recorded by a tail-flick analgesimeter (U. Basile, Italy). The beam intensity was adjusted to give a tail-flick latency of 2–3 s in the controls. To avoid tissue damage, a cut-off latency of 12–15 s was used.

The tail-flick reflex latencies of the mice (n = 32) were measured 60 and 30 min before the drug treatment, to determine basal values. The mice were then divided into four groups, and their tail-flick latencies were again tested 60 min after the oral treatment with vehicle or RHO at 10, 15 or 20 mg/kg. Each mouse was tested only once.

Statistical analysis. All the results obtained from the different tests are presented as mean ± SEM and compared against the control group using analysis of variance (ANOVA) followed by a *post hoc* comparison Newman-Keuls test. Statistical significance was set at $p < 0.05$.

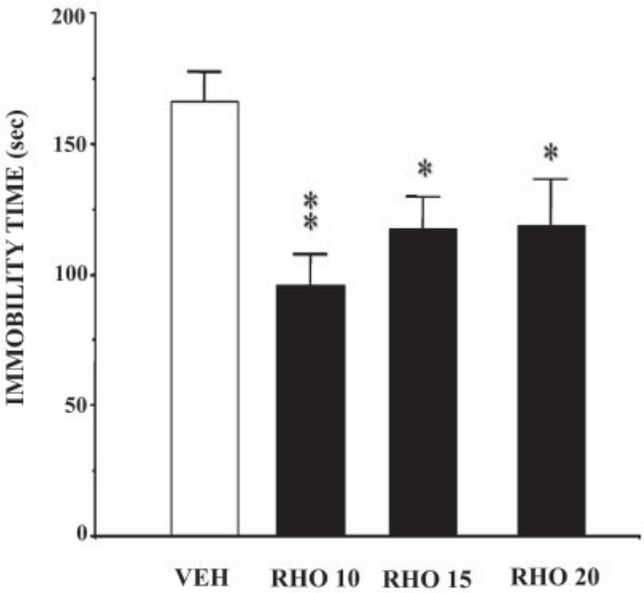

Figure 1. Immobility time in the forced-swimming test (over 6 min) in mice following i.g. administration of vehicle (VEH) and the *R. rosea* L. extract (RHO) at 10, 15 and 20 mg/kg. Data represent mean (± SEM) of 10 animals. Differences in RHO-treated from vehicle-treated: * $p < 0.05$, ** $p < 0.01$; where not indicated, the differences are not statistically significant.

RESULTS

Antidepressant-like activity

As shown in Fig. 1, in the forced-swimming test, the single i.g. administrations of RHO resulted in marked and statistically significant reductions in the total durations of immobility, at each dose tested. The effect was greater in the group treated with the lowest dose, of 10 mg/kg ($p < 0.01$). The analysis of variance confirmed the significant effects of RHO treatment [$F(3,36) = 6.219$; $p < 0.01$]. Also a lower dose of 5 mg/kg and a higher dose of 50 mg/kg were tested; both were not effective ([$F(2,23) = 0.748$; $p > 0.05$]; data not shown).

Adaptogenic activity: the swimming to exhaustion test

As shown in Fig. 2, the duration of swimming time over 20 min of exhaustive swimming was significantly increased in RHO-treated mice, compared with the control group. Analysis of variance confirmed the significant effect of treatment on the swimming time [$F(3,28) = 6.937$; $p < 0.01$]. A *post-hoc* comparison showed a statistically significant effect of RHO following administration of the intermediate dose of 15 mg/kg ($p < 0.01$), while doses of 10 and 20 mg/kg failed to reach statistical significance ($p > 0.05$).

Anxiolytic-like activity

Results of the light/dark test are shown in Table 1. The administration of RHO significantly increased the time spent in the light compartment (light time) [$F(3,28) = 3.084$; $p < 0.05$], the latency time for the first passage from the light compartment to the dark one (latency time) [$F(3,28) = 8.206$; $p < 0.001$], and the number of

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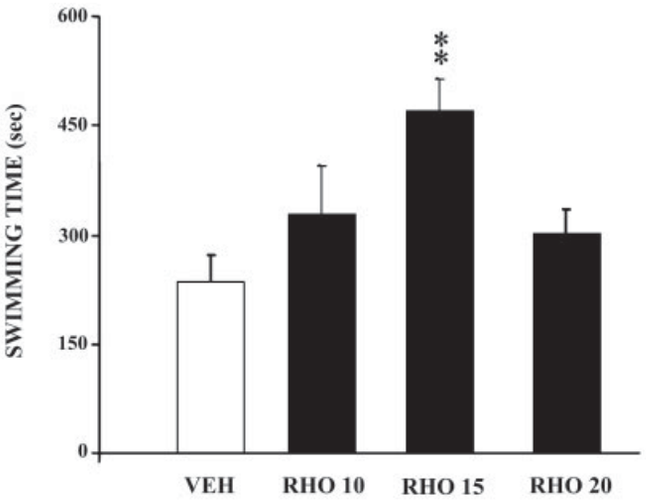

Figure 2. Swimming time in the swimming test to exhaustion (over 20 min) in mice following i.g. administration of vehicle (VEH) and the *R. rosea* L. extract (RHO) at 10, 15 and 20 mg/kg. Data represent mean (± SEM) of 8 animals. Differences in RHO-treated from vehicle-treated: ** $p < 0.01$; where not indicated, the differences are not statistically significant.

rearings [$F(3,28) = 7.651$; $p < 0.001$]. For each parameter analysed, the *post-hoc* analysis revealed a statistically significant effect at the lowest dose tested, of 10 mg/kg, and not at the higher doses of 15 and 20 mg/kg ($p > 0.05$). However, no changes were found in the number of entries into each compartment after administration of any of the RHO doses tested [$F(3,42) = 1.831$; $p > 0.05$].

Locomotor and anxiolytic-like activities

The overall effects of i.g. administration of RHO on the spontaneous motor activity of the mice in the open-field test are summarized in Table 2A. Statistical analysis revealed that the extract induced a significant, but not strictly dose-dependent, increase in total distance travelled [$F(3,32) = 4.106$; $p < 0.05$], in ambulation time [$F(3,32) = 4.246$; $p < 0.05$] and in rearing behaviour [$F(3,32) = 5.564$; $p < 0.01$], while it significantly reduced total resting time [$F(3,32) = 3.534$; $p < 0.05$]. The *post-hoc* analysis revealed a statistically significant effect only at a dose of 15 mg/kg ($p < 0.01$), whereas after lower and higher doses (10 and 20 mg/kg), no significant effects were seen ($p > 0.05$).

The analysis of anxiety-related parameters revealed marked alterations in the anxiety of the RHO-treated mice (Table 2B). Indeed, the time spent in the central area (central time) [$F(3,32) = 5.147$; $p < 0.01$], the central ambulation time [$F(3,32) = 4.172$; $p < 0.05$], and the central vertical activity (rearing) [$F(3,32) = 5.789$; $p < 0.01$] were significantly, but not dose-dependently, increased in the RHO-treated mice, compared with the control group. Conversely the number of fecal boli passed during the test was significantly decreased [$F(3,32) = 3.812$; $p < 0.05$]. The *post-hoc* analysis

Table 1. Effect of *Rhodiola rosea* hydroalcohol extract on behavioural parameters in the light/dark test in mice

Dose (mg/kg i.g.)	Light time	Latency time	Rearing	Entries
Control	69.25 ± 5.73	14.63 ± 1.94	11.13 ± 1.25	14.13 ± 1.34
10	87.50 ± 5.88[a]	20.25 ± 1.87[b]	14.88 ± 0.92[a]	17.00 ± 1.39
15	77.38 ± 6.22	11.50 ± 1.44	12.63 ± 1.16	13.00 ± 1.28
20	62.38 ± 6.77	8.75 ± 1.60	7.88 ± 0.88	12.88 ± 1.63

Data are mean ± SE of 8 animals for each group.
[a] $p < 0.05$; [b] $p < 0.01$ compared with control group.

Table 2A. Effect of *Rhodiola rosea* hydroalcohol extract on spontaneous locomotor activity in the open field test in mice

Dose (mg/kg i.g.)	Distance travelled (cm)	Ambulation time (s)	Rearing (*n*)	Resting time (s)
Control	1192 ± 103	71.16 ± 5.14	95.78 ± 12.27	188.67 ± 8.31
10	1437 ± 122	82.56 ± 5.45	115.89 ± 13.25	173.33 ± 6.31
15	1786 ± 148[b]	98.00 ± 5.53[b]	175.89 ± 19.66[b]	156.56 ± 6.95[a]
20	1371 ± 113	78.33 ± 5.89	116.11 ± 12.26	178.78 ± 6.88

Data are mean ± SE of 9 animals for each group.
[a] $p < 0.05$; [b] $p < 0.01$ compared with control group.

Table 2B. Effect of *Rhodiola rosea* hydroalcohol extract on anxiety-related parameters in the open field test in mice

Dose (mg/kg i.g.)	Central time (s)	Ambulation time (s)	Rearing (*n*)
Control	37.67 ± 4.31	17.22 ± 2.97	10.11 ± 4.90
10	30.56 ± 3.98	17.67 ± 3.73	9.33 ± 2.91
15	53.44 ± 3.98[a]	31.33 ± 3.89[a]	27.79 ± 4.90[a]
20	28.33 ± 3.14	18.78 ± 2.43	10.11 ± 3.59

Data are mean ± SE of 9 animals for each group.
[a] $p < 0.05$ compared with control group.

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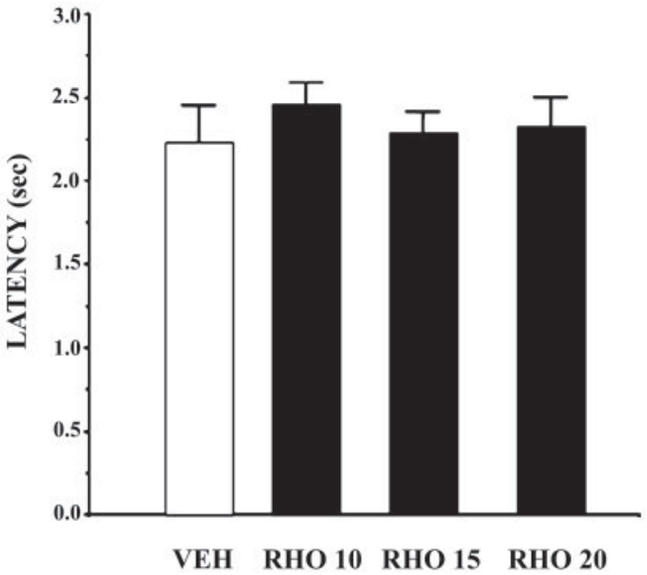

Figure 3. Tail-flick response latency 60 min following i.g. administration of vehicle (VEH) and three different doses of *R. rosea* L. extract (RHO) (10, 15 and 20 mg/kg). Data represent mean (± SEM) of 8 animals. No statistically significant differences were observed between the vehicle-treated and RHO-treated groups.

revealed a statistically significant effect only at the dose of 15 mg/kg ($p < 0.05$), and not at the doses of 10 and 20 mg/kg ($p > 0.05$).

Nociceptive assay

As shown in Fig. 3, no differences in the tail-flick reflex latencies were seen in the RHO-treated (10, 15 and 20 mg/kg) mice, in comparison with those of the control group. The analysis of variance confirmed there to be no significant effects of these treatments on nociception [$F(3,28) = 0.373$; $p > 0.05$].

DISCUSSION

The results of the present study provide evidence that the 3% rosavin and 1% salidroside *R. rosea* extract is able to induce antidepressant-like, adaptogenic, anxiolytic-like and stimulating effects in mice. Therefore, our data first confirm the efficacy of *R. rosea* extracts after a single administration, as seen by Panossian and Wagner (2005), and secondly confirm many preclinical and, particularly, clinical studies indicating adaptogenic and stimulating effects of such *R. rosea* extracts (Kelly, 2001; Brown *et al*., 2002; Zhu *et al*., 2003).

However, as far as we know, this is the first report showing antidepressant-like and anxiolytic-like activities for an *R. rosea* extract. Indeed, our results show that after single oral administration, RHO can significantly reduce the immobility time of mice in the predictive forced-swimming test; this finding clearly indicates that RHO can induce an antidepressant-like effect.

It is interesting to note that the RHO dose of 10 mg/kg was the most active in this forced-swimming test. Therefore, doses of the extract appear to be crucial to the types of effects obtained (Kelly, 2001). In line with this finding, Kurkin *et al*. (2003) reported that an extract of *R. rosea* at a dose of 10 mg/kg reduced the duration of thiopental-induced sleep in mice, whereas it increased the sleeping time at high doses (500 mg/kg).

It is known that depression is caused by a deficiency in the function of biogenic amines, e.g. serotonin, dopamine and norepinephrine. Consequently, the antidepressants act in many ways, through increasing the availability of these amines (Leonard, 1996).

Extracts of *R. rosea* have been reported to influence the levels and activities of biogenic monoamines, such as serotonin, dopamine and norepinephrine, in the cerebral cortex, brain stem and hypothalamus (Kurkin and Zapesochnaya, 1986). It is believed that these changes in monoamine levels are due to inhibition of the activities of the enzymes responsible for monoamine degradation (monoamine oxidase and catechol-*O*-methyltransferase), and to facilitation of neurotransmitter transport within the brain (Stancheva and Mosharrof, 1987). Therefore we can postulate that this antidepressant-like activity of RHO depends on its ability to enhance the catecholaminergic system (Burchfield, 1979; Lishmanov *et al*., 1987; Saratikov and Krasnov, 2004; Panossian and Wagner, 2005).

RHO also showed anxiolytic-like activities counteracting the anxiety in mice subjected to an aversive stimulus in two experimental models. In both models, the anxiolytic-like effect was again not strictly dose dependent. In the light-dark test, only the 10 mg/kg dose was active on mouse anxiety behaviour, while in the open-field test, the same dose failed to exert any significant anxiolytic effects, with the higher dose of 15 mg/kg needed for activity. Probably, this observed difference depends on the different sensitivities of the two experimental models used and on the main neurochemical mechanisms underlying the methods used.

It is known that numerous pathways are involved in the pathophysiology of anxiety states, and that a great number of neurotransmitters participate in the underlying mechanisms of this disease. Therefore, there are several anxiolytic substances that have different mechanisms of action, through GABA-ergic, serotoninergic and noradrenergic receptors (Prut and Belzung, 2003). It can be speculated that the ability of the *R. rosea* extract to enhance catecholaminergic transmission could be, at least in part, responsible for these anxiolytic-like effects of RHO.

However, the behavioural tests used here do not allow us to determine the exact mechanisms of anxiolytic effects or of the antidepressant effect of RHO, and therefore further appropriate studies are needed. In this regard, it has been reported (Lishmanov *et al*., 1987; Maslova *et al*., 1994) that *R. rosea* can reduce the secretion of corticotrophin-releasing factor (CRF), the major physiological mediator of stress (De Souza and Grigoriadis, 1994; Koob and Heinrichs, 1999). CRF also exerts an anxiogenic activity (Dunn and Berridge, 1990).

It has been demonstrated previously that RHO reverses the anorectic effects induced by intracerebroventricular CRF injection (Mattioli and Perfumi, 2005). Therefore the anxiolytic-like activities seen in the present study could also depend on this RHO ability to reverse the anxiogenic activity of CRF.

Our data also confirm the previously reported adaptogenic activity of *R. rosea* (Kelly, 2001; Brown

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et al., 2002; Zhu *et al*., 2003; Panossian and Wagner, 2005). Indeed, after single oral administration RHO increased the swimming time in the exhaustive forced swimming test, which represents a widely accepted pharmacological model for detecting adaptogenic activity.

Along with the anxiolytic effects, the adaptogenic effect of RHO was also statistically significant only at one dose (15 mg/kg). This finding strongly supports the concept that specific doses of these extracts are needed to obtain beneficial effects. Moreover, repeated dosing would probably induce significant improvements in the adaptogenic effects of RHO, as seen by Azizov and Seifulla (1998, article in Russian, reported by Kelly, 2001) in rats treated with an *R. rosea* extract.

Recently, Abidov *et al*. (2003) demonstrated that an extract of *R. rosea* very similar to that used in the present study significantly prolonged the duration of exhaustive swimming in rats and stimulated ATP synthesis in muscle during exercise. The authors postulated that these effects depend primarily on the rosavin complex. We speculate that in addition to an enhancing of the catecholaminergic system, the ability of RHO to increase the swimming time involves an improvement in cellular energy metabolism, based in part on ATP.

Finally, to explain the complex mechanisms underlying the adaptogen activity of RHO, the antioxidant effects of *R. rosea* should also be considered (Furmanowa *et al*., 1998; Boon-Niermeijer *et al.*, 2000; Battistelli *et al.*, 2005). Indeed, it is known that exercise generates free radicals when it is exhaustive (Vina *et al*., 2000) and that *R. rosea* is rich in phenolic compounds that can protect the nervous system from oxidative damage by such free radicals (Kelly, 2001; Brown *et al*., 2002).

It has been reported that adaptogenic activities of *Rhodiola* might also be due to an induction of opioid peptide biosynthesis and to an activation of both central and peripheral opioid receptors (Lishmanov *et al*., 1993). The data obtained in our nociceptive assay show no significant influences of RHO on nociception, which involves these opioid mechanisms. *R. rosea* extracts may interact with the opioid system only under stressful conditions. Indeed, *R. rosea* moderates the release of the opioid peptides that occurs as part of the pituitary–adrenal axis response to stress (Lishmanov *et al*., 1987). In this regard, it is known that stress induces antinociception and that adaptogens, including ginseng and the related ginsenosides, reduce this effect (Choi *et al*., 2003; Nguyen *et al*., 1995).

In conclusion, the present study provides original evidence that the single oral administration in mice of an *R. rosea* extract containing 3% rosavin and 1% salidroside elicits antidepressant, anxiolytic, adaptogenic and stimulating activities at the same time and across the same range of doses. Therefore, according to traditional medicine and some clinical studies with *R. rosea* extracts (Kelly, 2001; Brown *et al*., 2002; Zhu *et al*., 2003; Panossian and Wagner, 2005), these extracts can provide a very useful pharmacological tool for the treatment of depressive disorders that are combined with anxiety and other related nervous system conditions.

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