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EXPERIMENTAL PAPER

Influence of extracts from *Rhodiola rosea* and *Rhodiola kirilowii* on the development of alcohol tolerance in rats

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Summary

Introduction: *Rhodiola rosea* (RR) and *Rhodiola kirilowii* (RK) are well known for their influence on central nervous system, however their impact on the development of alcohol tolerance has not yet been proven.

Objective: The aim of this study was to determine the ability of RR and RK roots extracts to inhibit the

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development of alcohol tolerance *in vivo*, both, peripheral (metabolic) and central ones.

Methods: Male Wistar rats were treated with RR and RK extracts (*p.o.*) and ethanol (*i.p.*) for ten consecutive days. On the first, third, fifth and eighth days the hypothermic action of ethanol was measured, while on the ninth day the loss of righting reflex was examined. On the tenth day rats were treated with assigned extract and sacrificed 1 h after the ethanol injection.

Results: Both extracts inhibited development of tolerance to the hypothermic action of ethanol. The observed effect seems to be specific since none of the extracts affected body temperature in water-treated animals. RK extract also prolonged the hypnotic action of ethanol. RR-treated rats had higher blood-ethanol concentrations, in contrast to RK ones.

Conclusions: RR and RK extracts inhibited the development of tolerance to the hypothermic action of ethanol. Prolongation of the hypnotic action of ethanol by RK extract may be associated with influence on the central nervous system, while the RR one also inhibited the development of metabolic tolerance.

Key words: ***Rhodiola rosea, Rhodiola kirilowii, extracts, alcohol tolerance, rats, ethanol-induced hypothermia, sedative effect, blood alcohol concentration***

Słowa kluczowe: ***Rhodiola rosea, Rhodiola kirilowii, wyciągi, tolerancja alkoholu, hipotermia wywołana etanolem, działanie sedacyjne, stężenie alkoholu we krwi***

INTRODUCTION

Abuse and dependence on psychoactive substances remain one of a main social and economic issues in both developed and developing countries. For example, alcohol dependence generates an estimated cost for developed countries of 1.3–3.3% of their annual GDP (gross domestic product) [1]. Unfortunately, there is limited availability of clinically effective drugs that can be used in the treatment of addictions. In the case of alcoholism, only three medications are recommended by the EMA (European Medicines Agency) or FDA (Food and Drug Administration) – disulfiram, acamprosate and naltrexone (nalmefene in some countries) [2, 3]. The lack of therapeutic options legitimises seeking new substances that potentially may be used in the treatment of alcohol dependence and substances of plant origin seem to be an interesting alternative as well. *Salvia miltiorrhiza, Hypericum perforatum, Pueraria lobata* have received a great deal of attention from researchers in past years [4–8]. Other promising plants *are Rhodiola rosea* (RR) and *Rhodiola kirilowii* (RK) of the *Crassulaceae* family. These plants are well known in traditional medicine of Russia and Scandinavian countries with traditional medical indications including mild infections, altitude sickness, fatigue and depression [9]. In recent years, available reports were summarised in two meta-analyses with the conclusion that RR extract can increase physical and mental efficiency, although more randomised clinical trials are needed to confirm its properties definitively [10, 11]. Recently, an active compound of RR – salidroside – was proven to inhibit the development of alcohol tolerance in rats [12].

Therefore, the aim of this study was to examine an impact of RR and RK extracts in model of alcohol tolerance in rats.

MATERIALS AND METHODS

Animals

The experiment was performed on male Wistar rats kept in plastic cages (dim. 50x30x20cm), with five animals per one cage. Animals were provided with *ad libitum* access to fresh water and standard laboratory feed. Constant temperature (20±2°C) and humidity (60–65%) were maintained. During the experiment, a reversed 12 h light/dark cycle was established and all procedures were performed during the dark phase (the natural time for activity of these animals).

Reagents

Standardized water-ethanol (50/50%) extracts of the roots of RR and RK were used. Both extracts (*extractum siccum*) were provided by the Institute of Natural Fibres & Medicinal Plants in Poznań. Analysis of

dried extract of RR showed the presence of *p*-tyrosol (34±2 mg/100g), salidroside (90±2 mg/100g), rosarin (35±6 mg/100g), rosavin (147±35 mg/100g) and rosin (11±5 mg/100g). Analysis of dried extract of RK showed the presence of *p*-tyrosol (55±4 mg/100g) and salidroside (0.3±0.1 mg/100g). Other reagents applied in our experiment were of analytical grade, purchased from approved sellers.

Experimental protocol

The experiments were performed in accordance with Polish law and the Local Ethics Committee in Poznań (51/2015). The influence of RR extract on the development of alcohol tolerance was tested in 40 rats randomly divided into four groups. The influence of RK extract on the development of alcohol tolerance was tested in 46 rats, also randomly divided into four groups. At the beginning of the experiment, the body mass of each animal was noted and proper doses of reagents (ethanol and RR/RK extracts) were established. Body weighing was repeated on following days in order to correct the given doses. For ten consecutive days animals were intragastrically (*p.o.*) treated with the assigned extract at a concentration of 50 mg/ml in a dose of 500 mg/kg b.w., whereas control rats received a complementary volume of water (H_2O). One hour after treatment with the extracts, the animals were intraperitoneally (*i.p.*) injected with 30% ethanol (EtOH) at a dose of 3 g/kg b.w. or with water (H_2O) at a complementary volume. The development of alcohol tolerance was evaluated on the basis of the hypothermic and sedative action of ethanol. On the first, third, fifth and eighth day, the hypothermic action of ethanol was evaluated. The sedative effect was evaluated on the ninth day after challenging rats with ethanol at dose of 3.5 g/kg b.w. On the last, tenth, day, the animals were sacrificed by decapitation and blood-ethanol concentration analysis was performed.

Temperature measurement

Body temperature was measured four times on assigned days – once before treatment (T0) and at three time points after the administration of EtOH or H_2O (T30, T60 and T90 minutes after injection). Measurements were performed with a rectal thermometer. In the present study, temperature data are shown as the difference between T0 and each time point (delta). Most relevant differences were observed on the first and eighth day of the experiment, so for legibility the following figures include only these two days.

Loss of the righting reflex (LORR)

The duration of the ethanol-induced LORR was measured to examine the influence of both extracts on the sedative properties of ethanol. On the ninth day, immediately after the administration of ethanol, the animals were separately placed in cages in the supine position and left until recovery of the righting reflex (returns to normal position twice in one minute). The time of LORR (coma) was noted. Sleep duration was defined as a difference between the time of recovery and the time of losing the righting reflex.

Ethanol concentration

On the last day rats were sacrificed 30 minutes after ethanol administration and blood samples were immediately collected. 100 μl of each blood sample was mixed with 500 μl of 0.015% propionitrile (internal standard) and analysed by a Headspace GC. Sampling was performed with a Perkin Elmer AutoSystem XL GC with Headspace Sampler Turbomatrix 40.

RESULTS

Temperature measurement in RR group

The decrease in mean body temperature in H_2O+EtOH group at time points T60 and T90 were significant in comparison to the H_2O+H_2O group on the first ($p<0.01$) and eighth day ($p<0.0001$) as well (fig. 1–3). At time point T90 on the first day, the hypothermic effect in the RR+EtOH group was less clear than in the H_2O+EtOH group ($p<0.001$) (fig. 3). On the eighth day at time point T30, rats from the RR+EtOH group reached a significantly stronger decrease of body temperature than rats from the H_2O+EtOH group (fig. 1). Such a trend was also observed at time points T60 and T90, however, not significantly (fig. 2, 3).

What is more interesting, the decrease of temperature on the eighth day in the RR+EtOH group was also significantly more severe at all three time points than on the first day in this group ($p<0.01$). By contrast, in the H_2O+EtOH group on the eighth day at time point T90, we noted a significantly

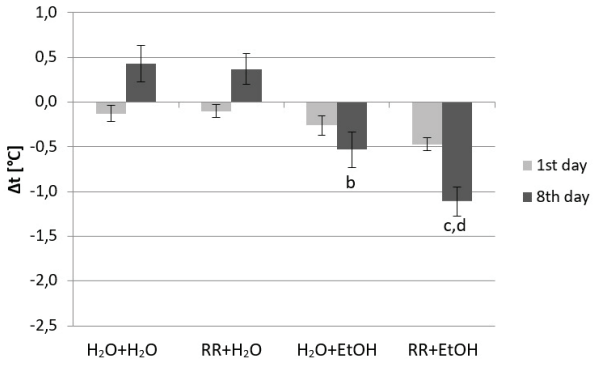

Figure 1.

Effect of *Rhodiola rosea* extract (RR) given at a dose of 500 mg/kg (*p.o.*) and ethanol administration (EtOH) (3.0 g/kg, *i.p.*) on the mean body temperatures of rats at time point T30.

Mean values ± SEM; b – $p<0.001$, different from the value in the H_2O+H_2O group; c – $p<0.01$, different from the value in the H_2O+EtOH group; d – $p<0.01$, different from the value on the first day in a given group. ANOVA interaction: $F(3,36)=8.50$; $p=0.0002$

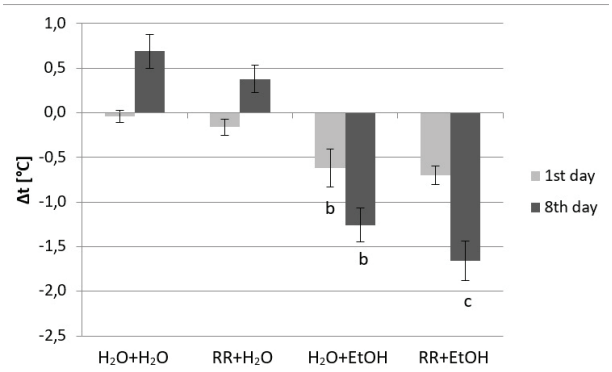

Figure 2.

Effect of *Rhodiola rosea* extract (RR) given at a dose of 500 mg/kg (*p.o.*) and ethanol administration (EtOH) (3.0 g/kg, *i.p.*) on the mean body temperatures of rats at time point T60.

Mean values ± SEM; b – $p<0.01$, different from the value in the H_2O+H_2O group on a given day; c – $p<0.01$, different from the value on the first day in a given group. ANOVA interaction: $F(3,36)=11.9$; $p=0.00001$

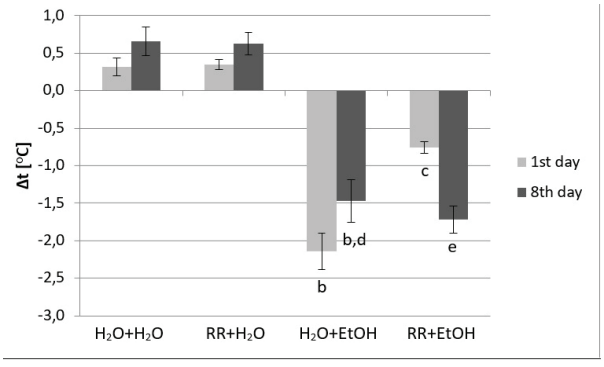

Figure 3.

Effect of *Rhodiola rosea* extract (RR) given at a dose of 500 mg/kg (*p.o.*) and ethanol administration (EtOH) (3.0 g/kg, *i.p.*) on the mean body temperature of rats at time point T90.

Mean values ± SEM; b – $p<0.001$, different from the value in the H_2O+H_2O group on a given day; c – $p<0.001$, different from the value in the H_2O+EtOH group; d – $p<0.01$, different from the value on the first day in a given group; e – $p<0.001$, different from the value on the first day in a given group. ANOVA interaction: $F(3,36)=9.06$; $p=0.0001$

less severe temperature decrease than on the first day (p<0.005). The RR+H_2O group did not differ in body temperature when compared with the H_2O+H_2O group on any day.

Temperature measurement in RK group

We observed that ethanol administration in the H_2O+EtOH group resulted in significant hypothermia after 60 and 90 minutes both on the first and eighth days (p<0.05) (fig. 4–6). In the RK+EtOH group, significantly less severe hypothermia than in the H_2O+EtOH group was observed after 60 and 90 minutes on the first day of the experiment (fig. 5, 6). Conversely, on the eighth day, rats from the RK+EtOH group suffered from significantly more severe hypothermia than rats from the H_2O+EtOH group at all three time points. The decrease in temperature in this group was also significantly more intense on the eighth day than on the first day. RK extract did not affect body temperature in the groups receiving water instead of ethanol.

Loss of the righting reflex (LORR)

On the ninth day, all groups (also the groups receiving water i.p. – as control rats) one hour after the administration of RR/RK/water were treated with intraperitoneal injection of ethanol at a dose of 3.5 g/kg b.m. in 30% *v/v* concentration (fig. 7, 8). The shortest duration of ethanol-induced LORR was observed in the H_2O+EtOH group, which differed significantly from the H_2O+H_2O. Rats from the RR+H_2O group slept longer than rats from the H_2O+H_2O group and rats from the RR+EtOH group slept longer than animals from the H_2O+EtOH group, however, differences were not significant (fig. 7). As for the part of the experiment concerning RK extract, in the H_2O+EtOH group a shorter duration of LORR than in the H_2O+H_2O group was observed (p<0.05) (fig. 8). In contrast, the RK+H_2O group was characterised by significantly longer sleeping time than the H_2O+H_2O group (p<0.03). Rats from the RK+EtOH group had a longer duration of LORR than rats from the H_2O+EtOH group, however, the difference did not reach significance.

Blood alcohol concentration (BAC)

Analysis of BAC was performed on the tenth day of the experiment. One hour after administration of RR/RK/water animals were treated with ethanol, and 1 hour later the rats were sacrificed (tab. 1). Significant differences between groups (ANOVA $F(1,14)=6.48$; p=0.02) were observed. Rats treated with RR extract (RR+EtOH) had a significantly higher BAC than rats from the H_2O+EtOH group (p<0.03). In the part of the experiment concerning RK extract, groups did not differ significantly in BAC (ANOVA interaction: $F(1,20)=1.47$; p=0.24).

DISCUSSION

The development of tolerance to ethanol action is one of the ICD-10 criteria for the diagnosis of alcoholism in humans. Thus, searching for new substances

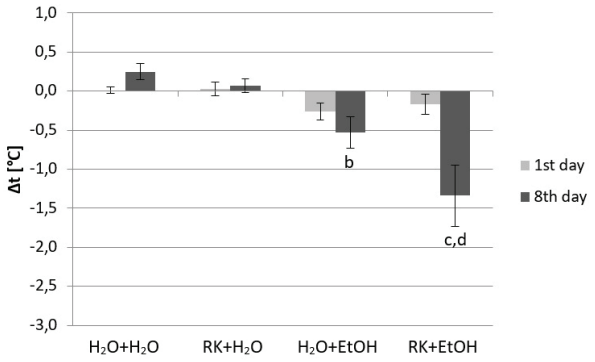

Figure 4.

Effect of *Rhodiola kirilowii* extract (RK) given at a dose of 500 mg/kg (*p.o.*) and ethanol administration (EtOH) (3.0 g/kg, *i.p.*) on the mean body temperature of rats at time point T30.

Mean values ± SEM; b – p<0.01, different from the value in the H_2O+H_2O group; c – p<0.01, different from the value in the H_2O+EtOH group; d – p<0.001, different from the value on the first day in a given group. ANOVA interaction: $F(3,40)=5.65$; p=0.002

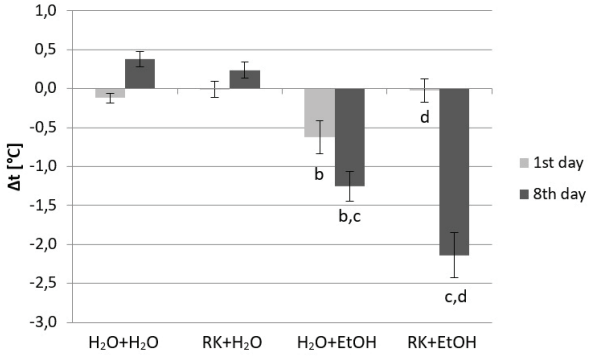

Figure 5.

Effect of *Rhodiola kirilowii* extract (RK) given at a dose of 500 mg/kg (*p.o.*) and ethanol administration (EtOH) (3.0 g/kg, *i.p.*) on the mean body temperature of rats at time point T60.

Mean values ± SEM; b – $p<0.05$, different from the value in the H_2O+H_2O group; c – $p<0.05$, different from the value on the first day in a given group; d – $p<0.01$, different from the value in the H_2O+EtOH group. ANOVA interaction: $F(3,40)=24.6$; $p=0.00000$

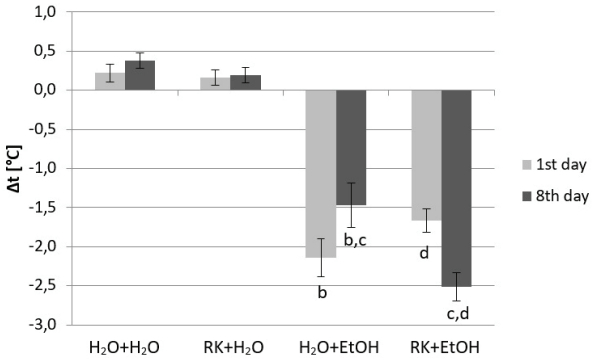

Figure 6.

Effect of *Rhodiola kirilowii* extract (RK) given at a dose of 500 mg/kg (*p.o.*) and ethanol administration (EtOH) (3.0 g/kg, *i.p.*) on the mean body temperature of rats at time point T90.

Mean values ± SEM; b – $p<0.001$, different from the value in the H_2O+H_2O group; c – $p<0.01$, different from the value on the first day in a given group; d – $p<0.05$, different from the value in the H_2O+EtOH group. ANOVA interaction: $F(3,40)=8.70$; $p=0.0001$

Table 1.

Effect of *Rhodiola rosea* extract (RR) and *Rhodiola kirilowii* extract (RK) given at a dose of 500 mg/kg (*p.o.*) on the blood-alcohol concentration on the tenth day, 1 h after ethanol administration (3 g/kg, *i.p.*)

	group	N	BAC [mg/ml]
Experiment RR	H_2O+EtOH	8	3.08±0.12
	RR+EtOH	8	3.40±0.04*
Experiment RK	H_2O+EtOH	11	2.88±0.20
	RK+EtOH	11	2.59±0.13

Mean values ± SEM

* – $p<0.05$, different from the value in the appropriate H_2O+EtOH group

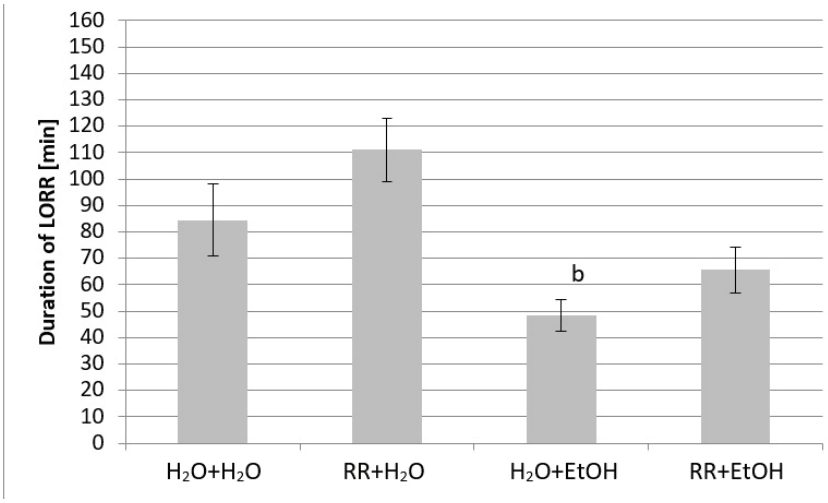

Figure 7.

Effect of *Rhodiola rosea* extract (RR) given at a dose of 500 mg/kg (*p.o.*) and ethanol (EtOH) at a dose of 3.5 g/kg (*i.p.*) on the duration of loss of righting reflex (LORR)

Mean values ± SEM; b – p=0.05, different from the value in the H_2O+H_2O group

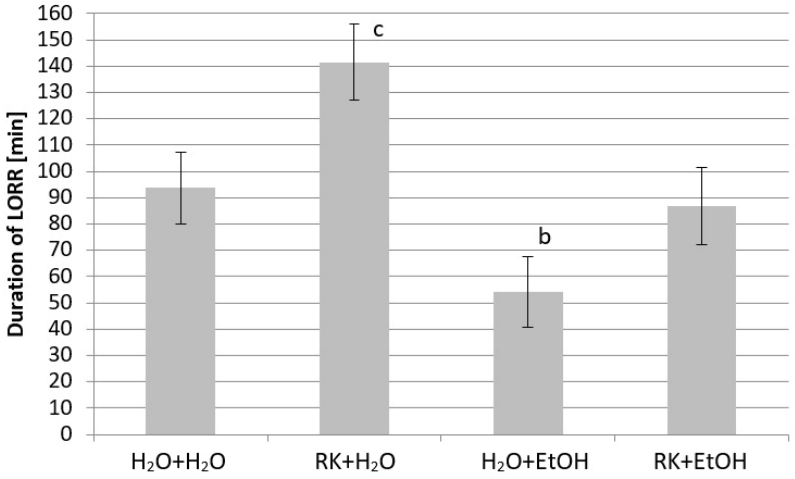

Figure 8.

Effect of *Rhodiola kirilowii* extract (RK) given at a dose of 500 mg/kg (*p.o.*) and ethanol (EtOH) at a dose of 3.5 g/kg (*i.p.*) on the duration of loss of righting reflex (LORR).

Mean values ± SEM; b – p<0.05, different from the value in the H_2O+H_2O group

that can inhibit its development seems to be justified. Alcohol tolerance is characterised by weakening the mainly aversive properties of ethanol as a consequence of repeated exposition to alcohol [13]. The appearance of distinctive effects varies in time and by monitoring the intensity of these effects it is possible to evaluate the degree of the development of tolerance. Our study is based on the assumption that daily administration of ethanol for ten days will produce such tolerance in Wistar rats, manifested by changes in the hypothermic and sedative action of ethanol. That model of alcohol tolerance, proposed by Crabbe, was successfully used some years ago in our department [14].

The aim of this study was to examine the ability of extracts from the roots of RR and RK to inhibit the development of acute ethanol tolerance. Use of these extracts was based on current scientific reports. It has been found that RR extract modulates 13 genes associated with substance abuse disorders, including eight directly connected with alcoholism [15]. RR extract is proven to prevent the establishment of morphine-induced conditioned place preference in mice [16]. Similar effects were observed in another

study, investigating the influence of RR and salidroside on nicotine-induced place preference in mice, where treatment with the extract before nicotine administration significantly reduced the development of conditioned place preference. The positive influence of RR extract was attenuated by co-administration of a selective 5-HT1 antagonist, which suggests the involvement of the serotonergic system in beneficial outcomes of RR [17, 18]. Our RR extract was standardised on *p*-tyrosol, salidroside and rosavin contents and administered to animals at daily dose of 500 mg/kg b.w. The dose was established on the basis of our previous studies and on data from studies mentioned above [19]. The RK extract was standardised on *p*-tyrosol and salidroside content. Basing on data from studies on the biological activity and chemical composition of RK, the extract was administered intragastrically at a dose of 500 mg/kg b.w. [19, 20].

In the current study, we observed development of alcohol tolerance in the both ethanol only treated (H_2O+EtOH) groups (from two independent *R. rosea* and *R. kirilowii* experiments). These groups had significantly higher mean body temperature on eighth day 90 minutes after the administration of ethanol than on the first day of the study. These results are in agreement with our above-mentioned study [14] on the development of ethanol tolerance in rats. On the first day we observed inhibition of the hypothermic action of ethanol in the RR+EtOH group – the decrease of mean body temperature of rats was significantly lower than in the H_2O+EtOH group. Hence, we hypothesised that the active compounds of RR extract interact with ethanol and weaken the pharmacodynamic action of alcohol. Concerning alcohol tolerance, after eight days of experiment we observed inhibition of its development in rats in RR+EtOH group, since on the eighth day, 90 minutes after ethanol administration, the mean body temperature in this group was significantly lower than on the first day and also lower, however insignificantly, than in the H_2O+EtOH group on the eighth day. Summarising, the administration of RR extract inhibited the development of tolerance to the hypothermic action of ethanol. We did not observe changes in mean body temperature in the RR+H_2O group when compared with the H_2O+H_2O group, thus we conclude that RR extract does not influence body temperature in normal conditions. Analysing the RK extract profile, similarly to RR activity, the ethanol-induced hypothermia effect was inhibited on the first day in the RK+EtOH group when compared with the H_2O+EtOH group and, in this way, weakens the pharmacodynamic action of alcohol, whereas repeated administration of RK extract inhibited the development of tolerance to the hypothermic action of ethanol in rats. The inhibition was the most marked on the eighth day, 60 and 90 minutes after ethanol injection, when the mean body temperature in the RK+EtOH group was significantly lower than in the H_2O+EtOH group and significantly lower than on the first day in this group.

The duration of LORR was examined on the ninth day when all groups were treated with ethanol at a 3.5 g/kg b.w. dose according to our previous experiments [21]. Rats from both H_2O+EtOH groups had a significantly shorter duration of LORR in comparison to the corresponding H_2O+H_2O group, which indicates the development of tolerance to the sedative action of ethanol. Rats from the RR+EtOH and RK+EtOH groups produced longer (however insignificantly) duration of LORR than animals in the H_2O+EtOH groups. In turn, the RK+H_2O group showed a significant longer duration of LORR when compared with the corresponding H_2O+H_2O group and the RR+H_2O group showed a longer (however insignificantly) duration of LORR than its H_2O+H_2O group. These effects can be explained by the sedative properties of these extracts and/or the active compounds themselves [22], however, there is also report that these extracts do not have such properties at the dose we used in our study [19].

The influence of RR and RK extracts on the pharmacokinetic tolerance to ethanol was also examined. On the tenth day, rats from the RR+EtOH group had a significantly higher mean BAC than rats from the H_2O+EtOH group. It means that RR extract affected alcohol metabolism and inhibited the development of pharmacokinetic ethanol tolerance. We did not observe such effect in the group receiving RK extract, what might be caused by the different content of active compounds in these two extracts.

RR and RK extracts did not affect body mass growth in normal conditions. All non-alcoholic groups were characterised by significant body mass growth, which did not differ between them. On the other hand, the repeated administration of ethanol resulted in significant inhibition of body mass growth in all alcoholic groups and RR and RK extracts did not prevent the anorexic effects of ethanol.

CONCLUSIONS

In conclusion, repeated exposure to ethanol at a dose of 3 g/kg b.w. for nine consecutive days resulted in the development of tolerance to the

hypothermic and sedative actions of EtOH in Wistar rats. The performed experiments also revealed the positive influence of RR and RK extracts on the course of alcohol tolerance in rats. Both extracts at a dose of 500 mg/kg b.w. inhibited the development of tolerance to the hypothermic effect of EtOH. At the same time, we did not observe the impact of these extracts alone on body temperature, which indicates the specificity of the pharmacological action. RK extract prolonged the sedative action of EtOH what can be associated with influence of this extract on central nervous system. RR extract elevated the ethanol concentration in blood, which means that RR extract has an impact on EtOH metabolism. Differences observed between these two extracts can be explained by different content of active compounds. As development of tolerance is one of ICD-10 criteria for alcoholism diagnosis, our results reveal that *Rhodiola* species are worth further investigation on that matter.

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Conflict of interest: Authors declare no conflict of interest

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