








Effect of solid herbal extract of *Primula veris* L. on the psychoemotional state of rats after chronic alcohol intoxication

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Abstract

Introduction: The aim of the study was the effect of solid herbal extract of *Primula veris* L. and comparison drugs phenotropil and mildronate on the psycho-emotional state of rats after chronic alcohol intoxication (CAI).

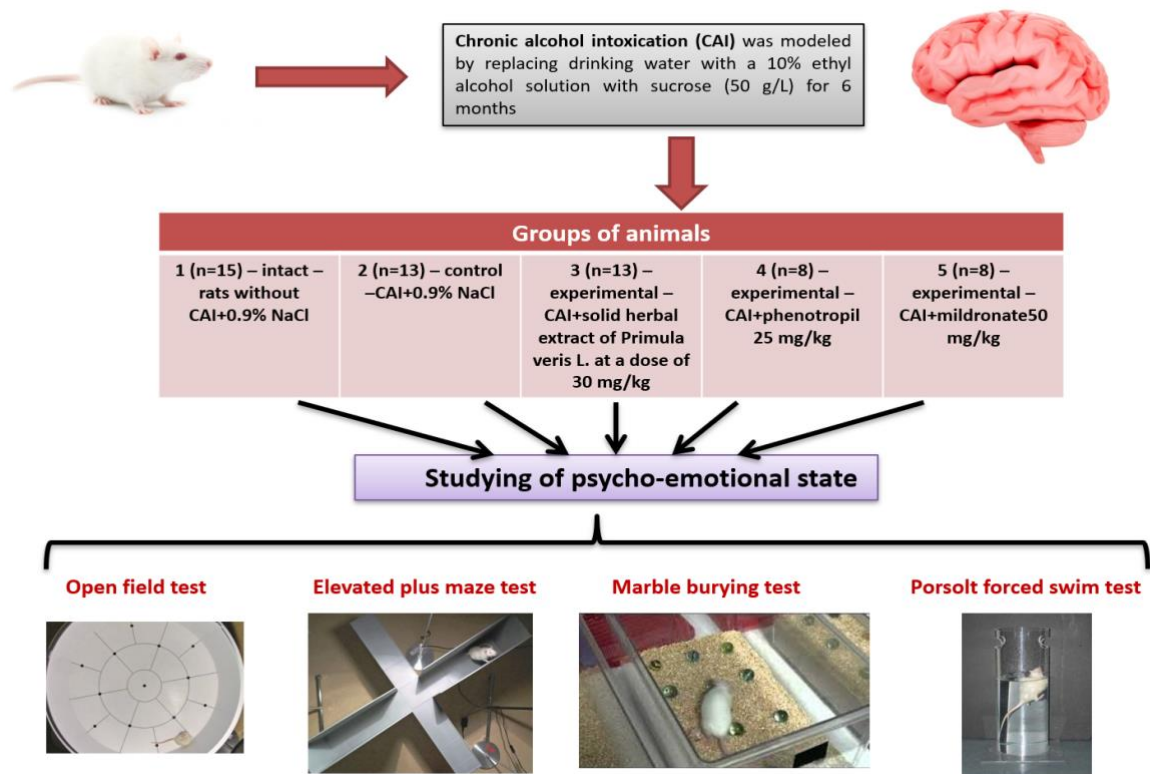
Materials and Methods: CAI was modeled by replacing drinking water with a 10% solution of ethyl alcohol with sucrose (50 g/L) for 6 months. After alcoholization, rats at the age of 16 months were divided into the following groups: 1 – intact – animals without CAI received oral 0.9% sodium chloride solution for 14 days; 2 – control – rats after ethanol withdrawal, which were injected with a 0.9% sodium chloride solution in a similar regimen; 3, 4 and 5 – experimental – females after CAI received oral solid herbal extract of *Primula veris* L. at a dose of 30 mg/kg, phenotropil 25 mg/kg, mildronate 50 mg/kg, respectively. After the end of treatment, to assess the psycho-emotional state of the animals, the Open field test, Elevated plus maze test, Marble burying test and Porsolt forced swim test were performed.

Results and Discussion: In animals after CAI, increased anxiety is observed, which manifested itself in a greater number of stands with support, urinations and boluses in the Open field test compared to the intact group. In the Elevated plus maze test, the trend remained the same: rats in the control group entered the open compartment installation less often, hung from it less often, and spent less time in the open compartment. In addition, females after CAI exhibited compulsive behavior in the Marble burying test. In the Porsolt forced swim test, animals in the control group had a shorter period of active swimming compared to intact females and a longer period of immobilization, which indicates depressive behavior in the former. Solid herbal extract of *Primula veris* L., phenotropil and mildronate contributed to the improvement of the psycho-emotional state of animals after CAI.

Conclusion: Thus, solid herbal extract of *Primula veris* L. at a dose of 30 mg/kg, which was administered orally once a day to female rats for 14 days after the withdrawal of ethanol, has a pronounced anxiolytic and antidepressant effect, while phenotropil and mildronate (25 mg/kg and 50 mg/kg, respectively, in a similar regimen) had a greater anticomulsive effect.



Graphical Abstract



Keywords

chronic alcohol intoxication, anxiety; compulsive and depressive behavior; solid herbal extract of *Primula veris* L.

Introduction

Alcohol consumption is a major risk factor for morbidity and mortality worldwide is well known (Ding et al. 2021). According to the World Health Organization, 237 million men and 46 million women suffer from alcohol use disorders (WHO 2018). According to Rosstat data, at the end of 2020, the prevalence of mental illnesses and behavioral disorders associated with alcohol use in Russia was 754.4 per 100,000 people among patients registered with treatment and preventive care facilities (Ageeva et al. 2021).

It should be noted that anxiety and depressive disorders occur in approximately 50% of patients with alcoholism (Anker et al. 2019). Chronic ethanol consumption is associated with structural and functional changes in the central and peripheral nervous system, related to direct and indirect damage to neurons and glial cells, demyelination, and disruption of neurotransmitter systems (Hammoud and Jimenez-Shahed 2019; Savage et al. 2021; Sushma et al. 2023; Wei et al. 2023).

Alcohol withdrawal leads to the development of abstinence syndrome, which contributes to sleep and cognitive impairment, anxiety, and depression. Moreover, depressive symptoms significantly correlate with anxiety during withdrawal (Sapkota et al. 2022). Researchers attribute this neurotoxic effect during alcohol withdrawal to disturbances in the glutamatergic system (Wiers et al. 2020; Siddiqi et al. 2023) and altered functioning of prefrontal neurons expressing the corticotropin-releasing factor 1 receptor (Patel et al. 2022).

Our previous studies demonstrated that solid herbal extract of *Primula veris* L. has endothelioprotective and antioxidant effects and improves mitochondrial function (Bychenkova

et al. 2018; Popova et al. 2018). Therefore, solid herbal extract of *Primula veris* L. holds promise for the treatment of the consequences of chronic alcohol intoxication (CAI).

Therefore, **the aim of this study** was to investigate the effects of solid herbal extract of *Primula veris* L. and comparison drugs phenotropil and **mildronate** on the psychoemotional state of rats after CAI.

Materials and Methods

Experimental animals

The study was conducted on 57 10-month-old female Wistar rats obtained from the Stolbovaya Laboratory Animal Nursery (Moscow region, Russia). Animals were maintained under 12-hour daylight conditions at a temperature of 21-22°C and humidity of 40-55% in the VolSMU vivarium. The experimental study was approved by the VolGMU Local Ethics Committee of the Russian Ministry of Health: Minutes No. 2022/138-DI dated May 6, 2022.

Modeling of chronic alcohol intoxication and treatment

CAI was modeled by replacing drinking water with a 10% ethyl alcohol solution with sucrose (50 g/L) for 6 months (Kryzhanovskij et al. 2019). After alcoholization, the rats at 16 months were divided into the following groups: 1 (n=15) – intact – animals without CAI, orally administered 0.9% sodium chloride solution for 14 days; 2 (n=13) – control – rats after ethanol withdrawal, which were administered 0.9% sodium chloride solution in a similar regimen; 3 (n=13), 4 (n=8) and 5 (n=8) – experimental – females after CAI, who orally received solid herbal extract of *Primula veris* L. at a dose of 30 mg/kg (the substance was provided by the Bashkir State Medical University, Russia, Ufa; the quality of solid herbal extract of *Primula veris* L. was standardized based on the content of **rutin**), phenotropil 25 mg/kg (the substance was provided by the A.I. Herzen State Pedagogical University, Russia, St. Petersburg), and **mildronate** 50 mg/kg (Grindeks, Latvia), respectively.

Assessment of the psycho-emotional state of animals

After completion of treatment, the following tests were carried out to assess the psycho-emotional state of the animals Open field test, Elevated plus maze test, Marble burying test and Porsolt forced swim test.

The Open field test was conducted for 3 minutes using a Stopwatch XL-5853 (China) in a circular rat cage of the same name (97 cm in diameter, Open Science, Russia). The number of crossed sectors, peering into holes, stances without support, stances with support, number of boluses and urinations were registered.

The Elevated plus maze test was conducted in a plus-shaped platform with two open (OA) and two opaque closed (OA) arms, each 50 cm long and 14 cm wide (Open Science, Russia). The latency period (LP) of exiting the central zone (CZ), the number of entries and the time spent in the OR and CZ, the number of stances and entrances in the OA, and the duration of the animal's stay in the CZ were registered over a 3-minute period using a Stopwatch XL-5853 (China).

In the Marble burying test, rats were placed in a 42 x 26 x 15 cm cage with a 5-centimeter layer of tightly packed sawdust for 30 minutes. Glass marbles were then arranged in the cage in a pattern of 4 rows of 5 marbles, and the rats were left in the cage for 30 minutes. The number of marbles buried (more than 2/3 of which were buried in the bedding) was then counted.

For the Porsolt forced swim test, rats were placed in transparent plastic cylinders (45 cm high, 20 cm in diameter, Open Science, Russia) filled with water to a distance of 10 cm from the rim (temperature 25±2°C). The LP of motor activity (the time from the moment the animal is immersed in a tank of water until the start of active swimming movements), the time of immobilization (the total time during which the animal “froze” while in the cylinder with water), and the active swimming time (the total time during which the animal performed active swimming movements while in a cylinder of water) were recorded for 3 minutes using a Stopwatch XL-5853 (China).

Statistical analysis

Statistical data analysis was performed using the GraphPad Prism 8 software package (GraphPad Software, USA). Normality of distribution was tested using the Shapiro-Wilk test. For normal distribution of the studied parameters, the Student's t-test was used to compare two groups and the Tukey test for multiple comparisons. For non-normal distributions, the Mann-Whitney test and the Kruskal-Wallis test (with Dunn) were used for paired and multiple comparisons, respectively. In addition, an assessment of the equality of variances (equal SDs) was performed; if the variances differed, the Brown-Forsythe and Welch tests were used. Differences were

considered statistically significant at $p < 0.05$. Data are presented as $M \pm SD$, where M is the arithmetic mean and SD is the standard deviation.

Results and Discussion

Control rats demonstrated decreased horizontal motor activity in the Open field test: the number of crossed sectors was 1.4 times ($p=0.0002$) lower than in intact females. Animals after CAI, who received saline solution, showed anxious behavior: the number of stances without support was 1.9 times ($p=0.0116$) lower, and the number of stances with support was 1.9 times ($p=0.0002$) greater compared to such in rats in the intact group. Furthermore, the number of boluses and urinations in control females was 1.9 ($p=0.0251$) and 2 times ($p=0.0157$) higher, respectively. A decrease in exploratory activity in females after CAI is indicated by a 1.8-time ($p=0.0017$) decrease in the number of times they looked into holes compared to such in the intact group.

In animals after CAI that received solid herbal extract of *Primula veris* L., phenotropil and *mildronate*, the number of crossed sectors was 1.5 ($p=0.0062$); 1.4 ($p=0.0316$) and 1.3 times higher, respectively, relative to the control group. This indicates an increase in horizontal motor activity. The studied substances helped to limit the animals' anxious behavior after CAI. The number of stances without support in rats that were administered solid herbal extract of *Primula veris* L. was 1.8 times ($p=0.0361$) higher compared to such in animals in the control group after CAI. The solid herbal extract of *Primula veris* L. and *mildronate* contributed to a decrease in the number of stances with support in females by 1.6 ($p=0.0036$) and 1.5 times ($p=0.0478$).

The number of boluses in rats administered solid herbal extract of *Primula veris* L., phenotropil and *mildronate* was 3.1 ($p=0.0059$); 6.1 ($p=0.0014$) and 6.1 times ($p=0.0012$), respectively, the number of urinations was 16.4 ($p<0.0001$); 5.24 ($p=0.0027$) and 2.62 times. In addition, the number of peering into holes in rats treated with solid herbal extract of *Primula veris* L. and phenotropil was 1.9 times greater ($p=0.0103$ and $p=0.0260$, respectively) relative to such in the control group (Fig. 1).

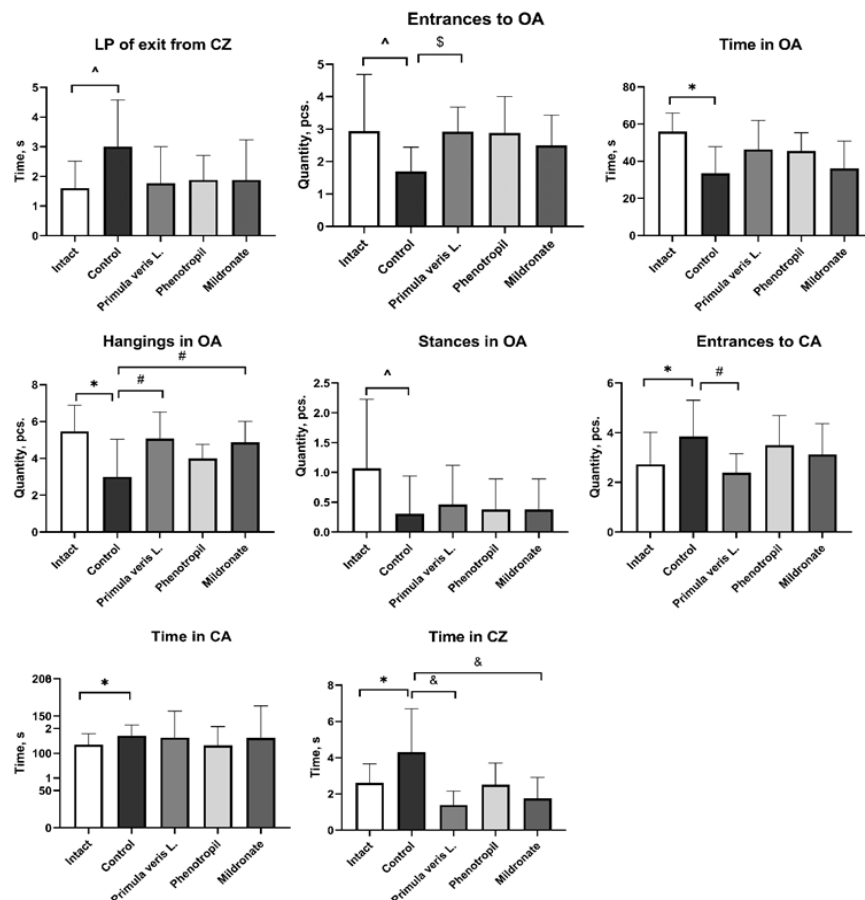


Figure 1. Behavioral activity parameters in the Open field test ($M \pm SD$). **Note:** Number of animals in groups: Intact ($n=15$), Control ($n=13$), *Primula veris* L. ($n=13$), Phenotropil ($n=8$), *Mildronate* ($n=8$). Differences are statistically significant relative to: * – intact group (Student's t-test); ^ – intact group (Mann-Whitney test); # – control group (Tukey test); \$ – control group (Kruskal-Wallis test (with Dunn)), $p < 0.05$.

The results of the Elevated plus maze test also indicate an increased level of anxiety in the control group animals compared to the intact group: the former entered the OA 1.7 times ($p=0.0261$) less often and spent 1.7 times ($p<0.0001$) less time in it compared to the intact group, the control group rats hung in the OA 1.8 times ($p=0.0009$) less often and reared in it 3.5 times ($p=0.0299$) less. The number of entries into the CA in rats after CAI that received saline was 1.4 times ($p=0.0413$) greater, and the time spent in the CA was 1.1 times less ($p=0.0382$).

In the Elevated plus maze test, solid herbal extract of *Primula veris* L. had an anxiolytic effect. The number of entries into the OA in rats after CAI that had been administered solid herbal extract of *Primula veris* L. and phenotropil was 1.7 ($p=0.0066$) and 1.6 times ($p=0.0436$) higher than in the control group. The number of entries into the CA in females receiving solid herbal extract of *Primula veris* L. was 1.6 times ($p=0.0167$) lower (Fig. 2).

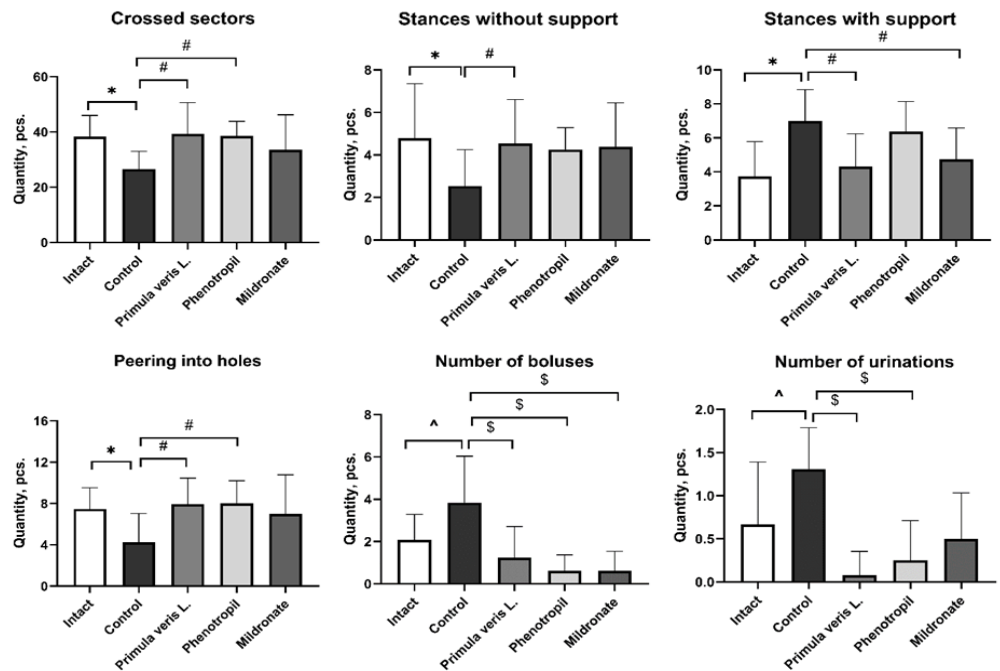


Figure 2. Behavioral activity parameters in the Elevated plus maze test ($M\pm SD$). **Note:** Number of animals in groups: Intact ($n=15$), Control ($n=13$), *Primula veris* L. ($n=13$), Phenotropil ($n=8$), *Mildronate* ($n=8$). LP – latency period, CZ – central zone, OA – open arm, CA – closed arm. Differences are statistically significant relative to: * – intact group (Student's t-test); ^ – intact group (Mann-Whitney test); # – control group (Tukey test); \$ – control group (Kruskal-Wallis test (with Dunn)); & – control group (Brown-Forsythe and Welch tests), $p<0.05$.

Females in the control group buried 1.7 times ($p=0.0320$) more marbles than in the intact group, indicating compulsive behavior in the former. Animals treated with phenotropil and *mildronate* buried 2 ($p=0.0353$) and 2.7 times ($p=0.0040$) fewer marbles than rats treated with CAI and saline solution (Fig. 3).

In the Porsolt forced swim test, the LP of motor activity in the control animals was 1.6 times ($p=0.0093$) higher than in the intact group, the immobilization time was 1.9 times longer ($p=0.0343$), and the active swimming time was 1.1 times shorter ($p<0.0001$). This indicates depressive behavior in the animals of the control group after CAI.

Solid herbal extract of *Primula veris* L. had an antidepressant effect – in rats administered solid herbal extract of *Primula veris* L., the LP of motor activity was 2 times ($p=0.0162$) lower than in the control group, and the active swimming time was 1.1 times ($p=0.0004$) longer (Fig. 4).

Long-term alcohol consumption is known to negatively impact the nervous system, which can clinically manifest as a range of anxiety disorders, depressive behavior, and cognitive dysfunction (Anker et al. 2019; Hammoud and Jimenez-Shahed 2019; Wołyńczyk-Gmaj et al. 2022; Wang et al. 2023).

In our study, animals after CAI exhibited increased anxiety in the Open field test, as evidenced by a greater number of stances with support, urinations, and boluses compared to the intact group. This trend persisted in the Elevated plus maze test – control rats entered the OA less frequently, spent less time hanging from it, and spent less time in the OA. Furthermore, female rats treated with CAI exhibited compulsive behavior in the Marble burying test. In the Porsolt forced swim test, animals in the control group had a shorter period of active swimming compared to intact females and a longer period of immobilization, which indicates depressive behavior in the former.

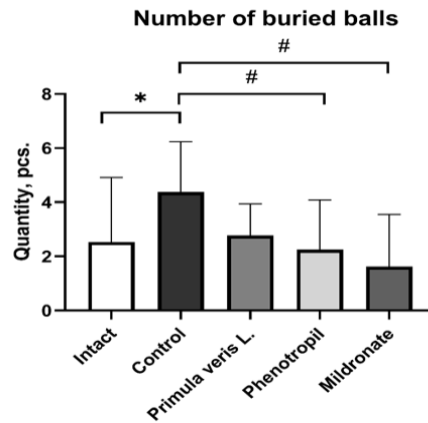


Figure 3. Behavioral activity parameters in the Marble burying test (M±SD). **Note:** Number of animals in groups: Intact (n=15), Control (n=13), Primula veris L. (n=13), Phenotropil (n=8), Mildronate (n=8). Differences are statistically significant relative to: * – intact group (Student's t-test); # – control group (Tukey test), $p < 0.05$.

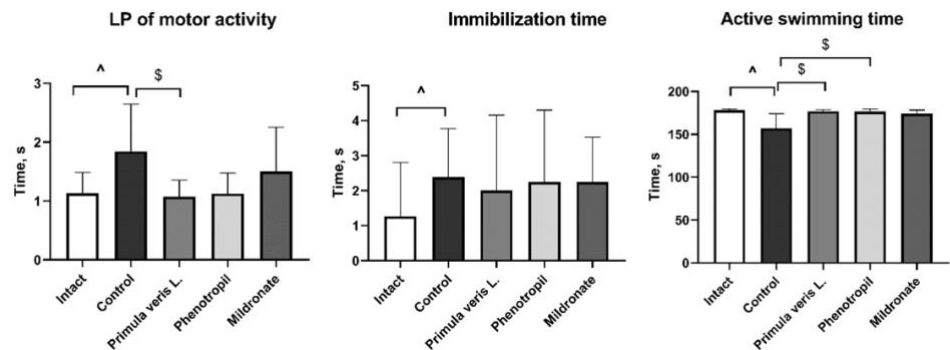


Figure 4. Behavioral activity parameters in the Porsolt forced swim test (M±SD). **Note:** Number of animals in groups: Intact (n=15), Control (n=13), Primula veris L. (n=13), Phenotropil (n=8), Mildronate (n=8). LP – latent period. Differences are statistically significant relative to: ^ – intact group (Mann-Whitney test); \$ – control group (Kruskal-Wallis test with Dunn's post-test), $p < 0.05$.

These psychoemotional disturbances are apparently related to the fact that chronic alcohol consumption is associated with a number of pathological mechanisms leading to neuronal damage. Ethanol exposure contributes to changes in the functioning of neurotransmitter systems – glutamate, GABA, serotonin, dopaminergic, and others (Gushcha et al. 2019; Yao et al. 2022). CAI leads to excitotoxicity due to the activation of glutamate receptors and decreased glutamate reuptake in the central nervous system, which is associated with mitochondrial dysfunction. The formation of reactive oxygen species triggers lipid peroxidation and damage to other important cellular structures, leading to apoptosis and neuronal necrosis (Kamal et al. 2020; Popova et al. 2021). Liu et al. (2022) demonstrated that CAI affects the transcriptome in the brain, particularly in the prefrontal cortex, which is responsible for planning complex cognitive behavior and decision-making. RNA sequencing analysis revealed that chronic alcohol consumption in C57BL/6J mice led to altered regulation of gene expression involved in mitochondrial energy metabolism, which was accompanied by increased anxiety in the animals and impaired short-term memory after ethanol consumption (Liu et al. 2022).

Solid herbal extract of *Primula veris* L., phenotropil, and mildronate contributed to the improvement of the psychoemotional state of animals after CAI. This effect of solid herbal extract of *Primula veris* L. is apparently due to its endothelioprotective and antioxidant effects, demonstrated in previously conducted experiments. The drug was found to improve mitochondrial respiration in cardiomyocytes under conditions of chronic heart failure (Bychenkova et al. 2018; Popova et al. 2018). Biological samples of blood plasma, heart cells, and cardiomyocyte mitochondria in rats administered solid herbal extract of *Primula veris* L. were shown to contain the flavonoid rutin (Smirnova et al. 2020). It has a pronounced antioxidant effect, exerts an anti-inflammatory effect, and increases microcirculation (Baratov et al. 2020), which may contribute to improved functioning of nervous system cells. According to the literature, mildronate, under hypoxia, reduces the transport of reactive fatty acids across

mitochondrial membranes and their accumulation against a background of decreased beta-oxidation intensity. Furthermore, **meldonium**, through the activation of acetylcholine receptors, stimulates the synthesis of NO in the vascular wall, exerting an endothelioprotective effect. Another mechanism of **mildronate's** neuroprotective effect is the limitation of oxidative stress and stimulation of the production of neurotrophic factors (Fedin et al. 2020; Kataev et al. 2025). Phenotropil is a nootropic drug that affects most neurotransmitter systems. It improves concentration and mental performance, increases brain tissue resistance to hypoxia and toxic substances, and has anxiolytic and antidepressant effects (Potupchik et al. 2019).

Conclusion

Thus, animals after CAI exhibited increased anxiety, depressive and compulsive behavior, as evidenced by the results of the Open field tests (a greater number of stances with support, urinations and boluses compared to the intact group), the Elevated plus maze test (rats in the control group entered the OA of the installation less often, hung from it less and spent less time in the OA), the Porsolt forced swim test (animals after CAI had a shorter period of active swimming compared to intact females and a longer period of immobilization) and the Marble burying test (animals in the control group buried more balls compared to the intact group).

Solid herbal extract of *Primula veris* L. at a dose of 30 mg/kg, phenotropil 25 mg/kg and **mildronate** 50 mg/kg, which were orally administered to female rats after CAI for 14 days, exerted anxiolytic and antidepressant effects, which were manifested by a higher number of stances without support compared to the control group, a decrease in the number of boluses and urinations in the Open field test; a higher number of hangings in the OA and fewer entries in the CA in the Elevated plus maze test; a lower LP of motor activity compared to the control group indicators and a longer period of active swimming in the Porsolt forced swim test. The most pronounced effect in these tests was noted with solid herbal extract of *Primula veris* L. In the Marble burying test, phenotropil and **mildronate** exerted an anticomulsive effect, as evidenced by a smaller number of buried marbles compared to the control group. In animals receiving solid herbal extract of *Primula veris* L., no statistically significant differences were found in this test compared to the control group.

Additional Information

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

This study did not receive any financial support from third parties.

Ethics statement

Animals were maintained under 12-hour daylight conditions at a temperature of 21–22°C and humidity of 40–55% in the VolSMU vivarium. The experimental study was approved by the VolGMU Local Ethics Committee of the Russian Ministry of Health: Minutes No. 2022/138-DI dated May 6, 2022.

Data availability

All of the data that support the findings of this study are available in the main text. Data corroborating the results of this study may be acquired from the corresponding author upon reasonable request.

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