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A Study of the Psychotropic Activity of Extracts of *Hedysarum Alpinum* L. and *Garcinia Mangostana* L

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Results: The test animals treated with *Hedysarum alpinum* L. extract demonstrated no significant change in the orientation and investigative behavior. The animals in the control group were given haloperidol, which appeared to have a distinctive inhibitory effect. The test animals in the *passive avoidance conditioning model* demonstrated a lower level of cognitive impairment under the influence of the pericarp extract of *Garcinia mangostana* L. This result can be associated with its positive effect on the emotional status, which plays an important role in memory trace formation. Phenazepam, on the contrary, had a negative effect on the formation and reproducibility of conditioned reflexes of aversive factor avoidance. The test group treated with *Garcinia mangostana* L. extract also showed no significant change in the orientation and investigative behavior compared to the control group.

Conclusion: Therefore, the extract of *Hedysarum alpinum* L. proved antipsychotic while causing no depressing effect. Thus, the extract of *Garcinia mangostana* L. possessed anti-anxiety activity and produced no depressing effect.

Keywords: Hedysarum alpinum L., Garcinia mangostana L., active avoidance conditioning, passive avoidance conditioning, open field test, antipsychotic effect, anti-anxiety activity.

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I. Introduction

Bad environmental conditions and stressful social situations increase the risk of neuropsychiatric disorders. As a result, neurotropic drugs, e.g. anxiolytics, antipsychotics, and psychostimulants, are becoming more and more marketable. Chlorpromazine was the first antipsychotic drug (1951) [7]. It was followed by anxiolytic drugs, e.g. diazepam, which appeared in 1963 [10]. These drugs marked the beginning of the psychopharmacology era. From then on, medical science has been striving to develop such a natural substitute for chemical medicinal products that would maintain pronounced therapeutic properties and produce no side effects.

Based on the neurobiological theory of consciousness, F. Crick, K. Koch [6], S. Gershon, and A. Eison defined the main properties of the “ideal” tranquilizer, or anxiolytic agent. First of all, it should possess a pronounced therapeutic effect, i.e. selective reduction of anxiety, and be innocuous. Second, it should not inhibit psychomotor functions, cognitive activity, attention, and memory. Finally, an ideal tranquilizer is non-toxic and does not aggravate the depressing side effects caused by other drugs [4].

As for the optimal spectrum of pharmacological activity, an “ideal” antipsychotic should be able to reduce positive symptoms, improve cognitive functioning, prolong remission, and prevent relapse. These properties should be combined with the highest possible level of innocuousness and no depressing effect [5].

Unfortunately, modern medicine possesses no psychotropic drugs that fully comply with the above criteria. Therefore, a search for phytogenic drugs with antipsychotic and anxiolytic properties remains relevant.

Chemical medicinal products currently used to treat mental disorders have a depressing effect. As a result, they produce a number of side effects, which

limits the possibility of their use, especially for patients whose work is associated with a longer-term attention span. Many antipsychotic drugs also produce a negative effect on cardiac activity, cause hyperprolactinemia (increased secretion of prolactin), suppress growth hormone, and trigger obesity and malignant antipsychotic syndrome [2].

Several Russian and foreign studies revealed psychostimulating, sedative, and anticonvulsant properties in plants of the *Hedysarum* and *Garcinia* genera [3, 8]. However, *Hedysarum* and *Garcinia* extracts proved to lack some of the side effects typical of chemical medicinal products. For instance, they did not produce the inhibitory effect that anxiolytics and anticonvulsants are known to have.

New drugs based on *Hedysarum* and *Garcinia* extracts will be efficient and without side effects. Therefore, their development is an urgent task, since they will be able to significantly improve the quality of life of patients during pharmacotherapy. However, while the chemical composition of these extracts received much scientific attention, their pharmacological properties remain largely understudied.

A study into the effect they produce on the cognitive functions and dopaminergic system seems to have a high scientific and practical potential. In this regard, passive and active avoidance conditioning tests can be especially informative. These tests make it possible to evaluate the effect of *Hedysarum* and *Garcinia* extracts on cognitive processes and predict their antipsychotic and anti-anxiety properties.

II. Materials and Methods

The present research featured dried 95% aqueous alcoholic tinctures of pericarp of *Garcinia mangostana* L. and aerial parts of *Hedysarum alpinum* L.

A set of experiments revealed the effect of the plant extracts on active avoidance conditioning, as well as orientation and investigative behavior of male Wistar rats during Open Field tests. Passive avoidance conditioning tests featured BALB\C male mice. All test animals were found conventional and of the first category. They were obtained from the Department of Experimental Biological Models of the E.D. Goldberg Research Institute of Pharmacology and Regenerative Medicine (Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russia). The tests were performed from 9am to 15pm. The animals were kept under standard vivarium conditions. They followed a standard feeding diet in accordance with the rules adopted by the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986).

The test samples were dissolved in purified water and administered to the animals intragastrically. The dose was 200 mg per 1 kg of body weight. The intact control group received purified water. The doses of haloperidol and phenazepam were 2 mg per 1 kg of body weight. These drugs were dissolved in purified water and used as comparators.

The antipsychotic effect was evaluated based on active avoidance conditioning model in a two-compartment shuttle chamber. The active avoidance conditioning lasted 2 days. The first session included 50 representations. The second session was conducted a day later and included 20 runs. One hour after it was administered the test sample or water (in the control group), the rat was placed in the first compartment. A sound signal followed 20 seconds later. Immediately, a light came on in the safe compartment. It served as the conditioned stimulus. The sound signal was followed by a 10-second delay-of-reward period. After that, an unconditioned stimulus in the form of impulse current was applied to compartment where the rat was sitting. The frequency was 5 pulses per second, while the amplitude slightly exceeded the threshold value and equaled 20-45V.

The threshold current values were defined individually. They were based on the animal's reaction marked with the start of squeaking. If the rat did not run into the illuminated safe compartment after the delay-of-reward period, it was given a series of electric shocks which persisted until the animal entered the safe compartment. The rat remained in the safe compartment for 15-90 seconds. The intervals were randomized to prevent habituation. After that, the procedure was repeated. The reaction was considered correct if the rat ran into the safe compartment before 10-second delay-of-reward period elapsed. The reflex was considered stable after nine out of ten consecutive correct reactions to the conditioned signal. The drug effect was evaluated in comparison with the control groups. The analysis also included interstimulus runs, i.e. switching compartments before the sound conditional signal [1].

The anti-anxiety effect was evaluated in terms of passive avoidance conditioning. The conditioning was conducted in a chamber that consisted of one large illuminated compartment and one small dark compartment. The animal was placed in the illuminated compartment. Due to the congenital preference for dark, it took the animal 10-20 seconds to move into the small dark compartment. After that, the door between the two compartments was closed. The floor of the dark compartment contained parallel alternating electrodes. When the animal was in, it was given electric current pulses. Each pulse lasted 50 msec with a frequency of 5 Hz and amplitude of 50 mA. After 10 sec, the door was opened and the animal was allowed to move into the safe illuminated compartment. As a result, the animal developed a conditioned reflex of dark space avoiding. To check the reproducibility, the animal was placed in the illuminated compartment in the corner opposite to

the door to the dark compartment and observed for three minutes. The experiment registered the time of the first entry into the dark compartment, i.e. the latent time of entry, and the total time spent in the dark compartment. The reflex was considered stable if the animal did not venture into the dark compartment for three minutes, or if the latent time exceeded 150 sec. The quality of the reflex was assessed according to the share of the animals that developed it. The experiment included several additional indicators that described the conditioned reflex and behavioral status, i.e. the number of entries into the dark compartment, the time spent in the dark compartment, and partial entry into the dark compartment [1].

The side depressive effect of the extracts was evaluated based on the behavior of the animals during the Open Field test [9]. The degree of the depressive effect depended on the degree of inhibition of investigative activity. The Open Field test was performed in a chamber of 100x100x40 cm with white walls. Its floor was divided into 16 squares. Each square had a circular hole (3 cm in diameter). The chamber was illuminated by an electric incandescent lamp with a 100-watt light bulb placed 1 m above the floor. The rat was put in a corner and observed for three minutes. There were two check-lists: one for the first minute and one for the two remaining minutes. The check-list registered the number of movements from square to square (horizontal activity), the times the animal stood on its hind legs (vertical activity), sniffing and hole exploration (hole exploratory behavior), washing (grooming), and bowel movements (number of droppings). The skewness ratio in the behavior (%) was calculated as the ratio of the number of horizontal movements vs. the total physical activity. The results of the first minute and two subsequent minutes of testing were evaluated separately and together.

III. Results and Discussion

The active avoidance conditioning was successful in the control rats. The animals demonstrated the reflex after 24 hours (Fig. 1).

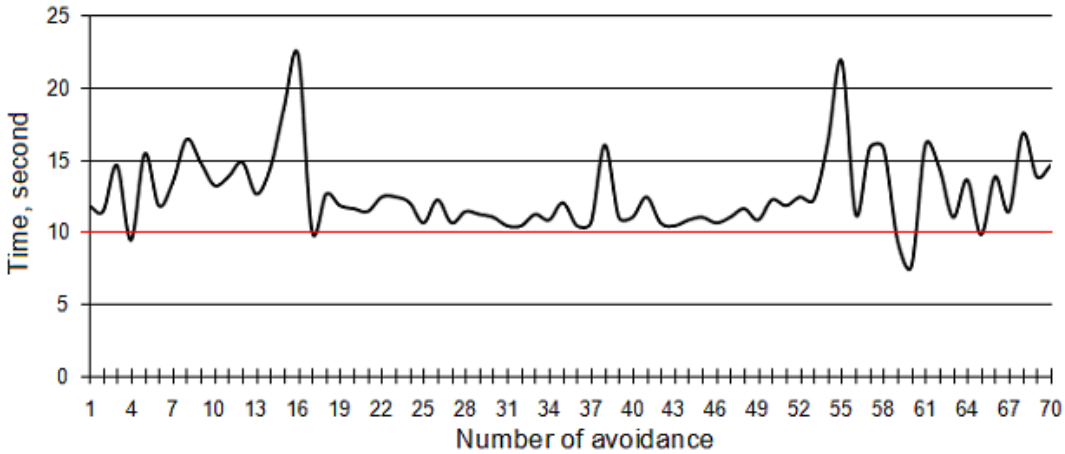

Fig. 1: Acquisition of the Active Avoidance Conditioned Reflex in the control group

After administration of haloperidol, the animals did not avoid the electric pain stimulus and demonstrated a longer latency period when moving to the dark compartment (Fig. 2).

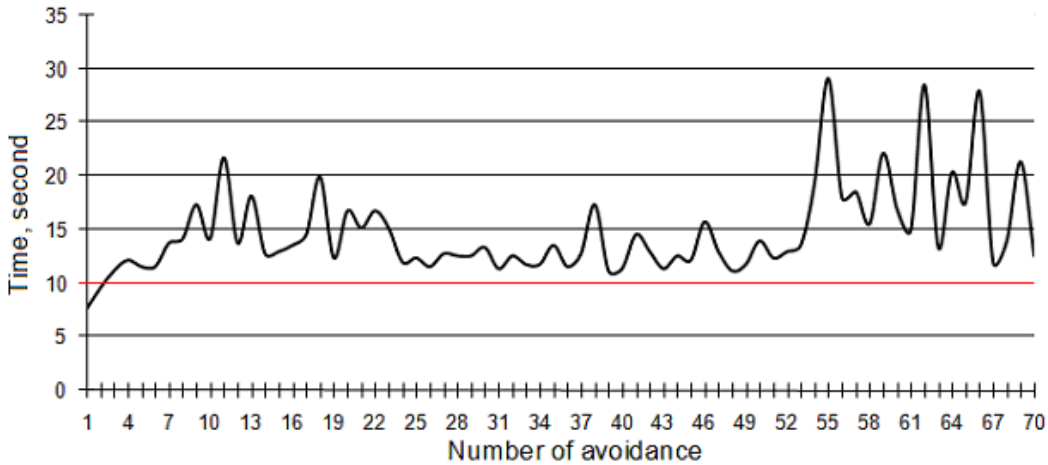

Fig. 2: The Effects of Haloperidol on Acquisition of the Active Avoidance Conditioned Reflex

The active avoidance conditioning resulted in a significant increase in the latency period that preceded the entry into the dark compartment in the animals treated with the *Hedysarum alpinum L.* extract compared with the control group and the comparison group where the animals were given haloperidol as a common antipsychotic (Fig. 3).

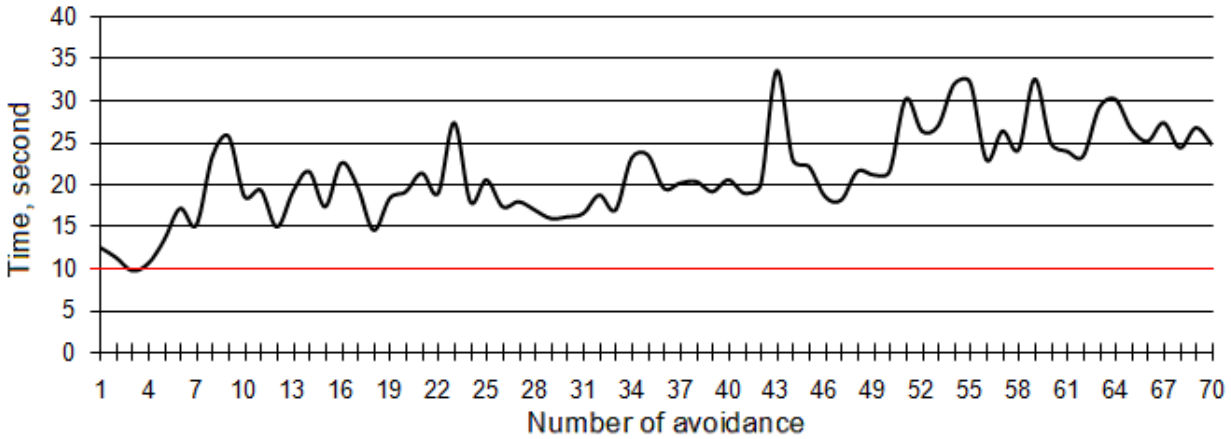

Fig. 3: The effect of herb extract of *Hedysarum alpinum* L. on Acquisition of the Active Avoidance Conditioned Reflex

Thus, the extract of *Hedysarum alpinum L.* proved to have a more pronounced effect on dopamine-induced changes in animal behavior compared to such popular antipsychotic as haloperidol.

The animals treated with the pericarp extract of *Garcinia mangostana* L. demonstrated a significantly lower ability to develop active avoidance reflex, compared with the control group. The animals did not avoid electrical impulses and moved to the safe compartment immediately after being exposed to electricity, while the function of reward prediction had obviously been affected (Fig. 4).

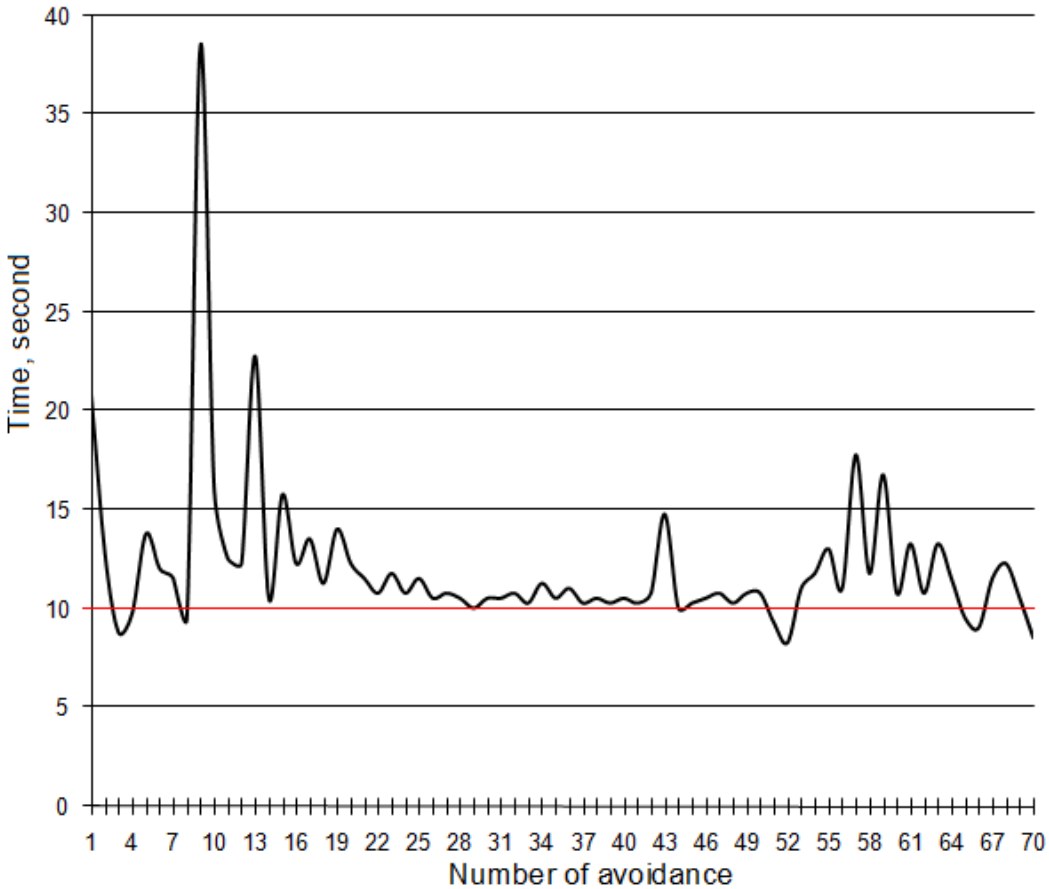

Fig. 4: The effect of pericarp extract of *Garcinia mangostana* L. on Acquisition of the Active Avoidance Conditioned Reflex

After administering the pericarp extract of *Garcinia mangostana* L., the depressed activity in the system of goal achievement was accompanied by a lower level of neurotic resistance. These effects may be due to the fact that the pericarp extract of *Garcinia mangostana* L. blocks postsynaptic receptors and thereby disrupts dopaminergic transmission of nerve impulses in various parts of the central nervous system.

The processes of development and reproduction of conditioned passive avoidance reflex is the most common experimental technique used to study memory, as well as the development and stability of conditioned reflexes. In this case, the behavioral essence of the reflex is a conflict between the congenital-to-rodents reflex of dark space preference and the acquired conditioned reflex of avoiding the electric pain stimulus inflicted in this dark space during conditioning. Table 1 shows the effect of plant extracts on passive avoidance conditioning.

Table 1: The effect of plant extracts on Acquisition of the Passive Avoidance Conditioned Reflex

Group	Conditioning	24 h			7 days		
	1 entry, sec	1 entry, sec	Number of entries	Time spent in the dark compartment, sec	1 entry, sec	Number of entries	Time spent in the dark compart-ment, sec
Control group	15.6± 2.61	161.9± 9.55	0.6± 0.27	4.5± 2.11	138± 17.05	0.9± 0.4	8.2± 4.86
Phenazepa-mum	54.9*± 21.12	130.3*± 22.42	1.1*± 0.48	38.1*± 19.78	147.7*± 21.56	0.3*± 0.21	31.6*± 21.08
Extract of *Hedysarum alpinum* L.	34.1*± 17.4	133*± 17.13	1.7*± 0.54	23.1*± 10.42	122.7*± 19.5	2.0*± 0.7	19.9*± 6.15
Extract of *Garcinia mangostana* L.	26.1*± 2.9	150.9± 13.9	1.5*± 0.33	12.5*± 5.6	141.3± 16.19	1.1± 0.48	12*± 5.53

*Notes: Controls received distilled water; the number of animals in each group was n = 10 (total number of animals = 40); *p < 0.05.*

The animals that were given extracts of *Hedysarum alpinum* L. and *Garcinia mangostana* L. had a larger number of entries into the dark compartment, while the time they spent there decreased, compared with the group of animals treated with phenazepam. Not only do animals under stress demonstrate an anxiodepressive state, but they also show a definite decline of cognitive function. The animals treated with phenazepam demonstrated a pronounced cognitive impairment, i.e. the latent period of the first entry into the dark compartment decreased while the number of entries increased. Moreover, the animals treated with phenazepam were more depressed: they spent more time in the dark compartment. The animals treated with *Garcinia mangostana* L. extract and, to a lesser extent, those treated with the extract of *Hedysarum alpinum* L., showed better learning skills and memory during the test. The animals treated with the pericarp extract of *Garcinia mangostana* L. proved to have the most stable reflex.

The lower cognitive impairment in the animals treated with *Garcinia mangostana* L. may be associated with the positive effect the extract has on the emotional status, which contributes to better memory trace formation. As for phenazepam, it had a negative effect on the development and reproducibility of conditioned reflexes of aversive factor avoidance. The Open Field test provides a typical acute stress environment (stress of novelty), accompanied by adaptation to new conditions. Novelty stress generalizes exaltation and increases anxiety. When placed in unfamiliar environment, the animal activates behavior due to its natural curiosity, which is an unconditioned self-development reflex. This activation is intensified by anxiety, i.e. fear, or stress, of novelty. The system of behavioral inhibition manifests itself through anxiety. Its main function is to monitor the success of current activities. In the Open Field environment, the system of behavioral inhibition has an ambivalent effect on behavior indicators: the high level of anxiety suppresses investigative activity, while its low or medium level activates the behavior Fig. 5 illustrates the orientation and investigative behavior under the Open Field conditions.

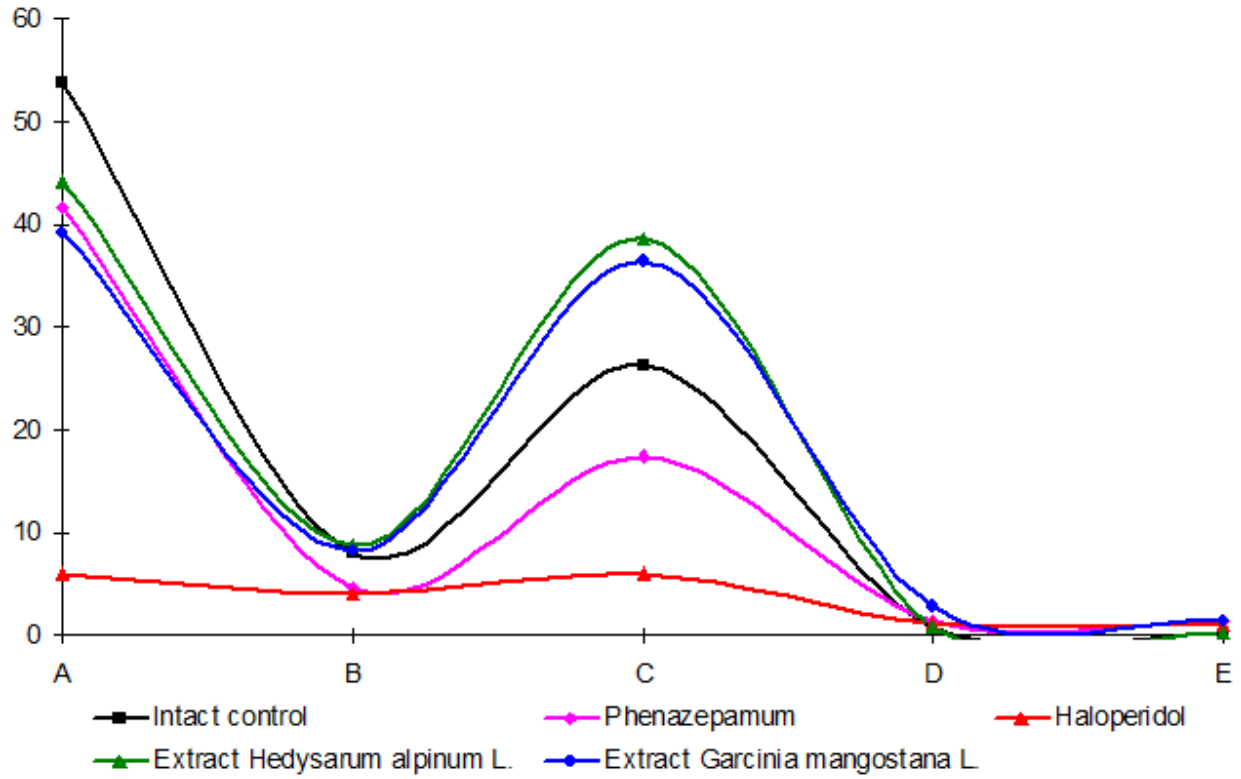

Fig. 5: Effect of plant extracts on the approximate research behavior of mice in the open field test: A - Horizontal activity (number of times the line of a square is crossed with all 4 legs); B - Vertical activity (number of times the animal stands on its hind legs); C - Research reflex (number of peeping and sniffing holes); D - Grooming (frequency of grooming activity); E - Defecation (number of defecation boli)

The animals treated with haloperidol clearly experienced its inhibitory effect on orientation and investigative behavior. The animals treated with phenazepam also demonstrated a lower orientation and investigative activity, compared with the control group, but not as low as in the haloperidol group.

The extract of *Hedysarum alpinum* L. and the pericarp extract of *Garcinia mangostana* L. lowered the horizontal activity index and boosted the investigative activity index, compared with the control group. The research revealed no depressing effect in the plant extracts of *Hedysarum alpinum* L. and *Garcinia mangostana* L.

IV. Conclusion

The experiment proved that the extract of aerial parts of *Hedysarum alpinum* L. had antipsychotic properties while showing no depressing effect. The pericarp extract of *Garcinia mangostana* L. improved the conditioned reflex activity in the test animals after passive avoidance conditioning, which also indicates antianxiety activity and no depressing effect.

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