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# Evaluating the Therapeutic Potential of Neurotropic Biocomplexes in Alzheimer's Disease: A Biotechnology Perspective

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## Abstract

This study investigates the potential of novel biocomplexes derived from maral antlers (Pantobiol-4 formulations) to counteract cognitive impairment in a rat model of Alzheimer's disease (AD) induced by amyloid-beta 25-35 injection. Three Pantobiol preparations (Pantobiol-4-1, Pantobiol-4-2, and Pantobiol-4-3) were evaluated at different doses using behavioral (novel object recognition and passive avoidance) and biochemical [choline acetyltransferase (ChAT) activity, testosterone, and dehydroepiandrosterone (DHEA) levels] analysis. The experiments demonstrated the effectiveness of the Pantobiol-4 group in restoring central nervous system functions impaired by beta-amyloid toxicity, targeting the basal nucleus. The results show that Pantobiol-4 therapies, especially Pantobiol-4-3, can considerably improve learning capacities, normalize cholinergic function, and restore cognitive function, as evidenced by improved performance in behavioral tests and restoration of ChAT activity. Pantobiol-4 formulations also modulated testosterone and DHEA levels altered by beta-amyloid. The normalization of DHEA content observed with Pantobiol-4 treatments suggests a potential antioxidant component. The data obtained indicate a wide range of biological activity of the tested biocomplexes and the specific nature of their effects on cognitive functions, confirming that their complex protective action may include antioxidant effects. Analysis of the behavioral and biochemical data supports that Pantobiol-4 formulations hold promise as therapeutic agents for mitigating cognitive deficits associated with neurodegenerative diseases.

**Keywords:** Alzheimer's disease, Neuroprotective, Biocomplex, Maral antlers, Cognitive impairment, Choline acetyltransferase

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## Introduction

Progressive cerebral atrophy and debilitating dementia are the hallmarks of Alzheimer's disease (Lane *et al*., 2018; DeTure & Dickson, 2019; Amanvermez & Hueting, 2020). Despite the prevalence of this condition, reliable preventive strategies and pharmacological treatments remain under-researched, necessitating the exploration of innovative neurotropic compounds (Jack, 2018; Livingston, 2020; Alzheimer's Association, 2023). Targeted metabolic support using biologically active complexes represents a promising avenue in neurobiology (Molnar & Arnold, 2021; Sharma *et al*., 2021). This investigation seeks to quantify the neuroprotective properties of a specialized dietary supplement synthesized from maral (Cervus elaphus) antlers within an AD-simulated environment.

*The Primary Objectives Include*

- Determining the efficacy of pantohematogen-based agents (20 and 45 mg/kg) in alleviating cognitive impairment following amyloid-induced damage to the Meynert nucleus.
- Quantifying changes in ChAT activity as a proxy for cholinergic fiber integrity in the cortex (Hampel *et al*., 2019; Knopman *et al*., 2021).
- Analyzing the regulatory influence of these biocomplexes on systemic testosterone and dehydroepiandrosterone (DHEA) concentrations (Nave *et al*., 2017; Sundermann, 2020; Zitzmann, 2020; Gong, 2021; Janati, 2021; Papadopoulos & Li, 2022).

## Materials and Methods

The study utilized male Wistar rats (sourced from the RAMS Stolbovaya facility). Animals were maintained under standardized laboratory protocols with uniform dietary intake and housing. The subjects were categorized into eight distinct groups (n=10 per group):

Sham-operated: Surgical control.

AD-Control: Amyloid-beta 25-35 injected, plus vehicle (water). 3-8. Experimental: AD model treated with Pantobiol variants (4-1, 4-2, 4-3) at low (20 mg/kg) or high (45 mg/kg) dosages.

Treatments were administered via gastric intubation. Cognitive assessments began after a recovery period, utilizing indices of novel object interaction and passive avoidance response.

The test substance, Pantobiol, is a product of proprietary processing of maral antler powder. Its chemical profile is multifaceted, containing insulin-like and nerve growth factors (IGF, NGF), essential amino acids, phospholipids, and a spectrum of vitamins and minerals. Notably, it includes precursors for steroid hormones and regulatory peptides (Armstrong, 2019; Goedert & Spillantini, 2019; Hampel *et al*., 2019; Wu *et al*., 2022).

*Research Methods and Models*

*Pathology Simulation*

AD-like symptoms were induced by stereotactic delivery of the 25-35 beta-amyloid fragment into the Meynert nucleus. This procedure replicates the cholinergic deficit and memory loss characteristic of human AD (Scheltens, 2021; Kandimalla & Reddy, 2022; Li, 2023). Injections used a microsyringe (coordinates: AP-1.5, DL ±2.7, H 8.1).

*Behavioral Assessment*

*Object Recognition*

Animals were evaluated over three sessions to calculate a "Recognition Index." Memory was gauged by the animals' preference for an unfamiliar object over a known one.

*Passive Avoidance*

Testing involved the suppression of the natural tendency to enter a dark chamber after receiving an aversive electrical stimulus. Long-term memory was measured by the latency of entry during subsequent trials.

*Biochemical Analysis*

Post-sacrifice, Choline Acetyltransferase (ChAT) activity was analyzed in cortical homogenates using the Fonnum radiometric method. This involves tracking the synthesis of labeled acetylcholine. Hormonal quantification (Testosterone/DHEA) was performed using ELISA (DRG Diagnostics) on blood serum collected 24 hours post-treatment.

## Results and Discussion

The results of the study are presented in **Table 1**, which reflects the influence of the tested drugs on the behavioral indicators of animals in the object recognition model.

**Table 1.** Study of the effect of dietary supplements on indicators of orientation-research activity and long-term memory in the object recognition model

| Animal Groups | Total time spent exploring objects during an exploration session(s) | Total time spent exploring objects in the testing session(s) | Time of exploration of the "old" object in the testing session(s) | Time of exploration of a "new" object in the testing session(s) | Recognition Index (%) |
|---|---|---|---|---|---|
| 1. Sham operation | 17.8±2.0 | 15.6±7.2 | 3.8±2.4 | 11.8±5.3 | 52.3±21.3 |
| 2. Control | 14.0±3.9 | 13.0±3.9 | 6.3±1.9<br>* p=0.012 | 6.8±2.5<br>* p=0.043 | 3.1±20.9<br>* p=0.001 |
| 3. Pantobiol-4-1 45 mg/kg | 8.8±3.5<br>* p=0.008 | 8.2±2.9<br>* p=0.034 | 2.3±1.2<br>* p=0.001 | 5.9±2.0<br>* p=0.009 | 49.9±22.8<br># p=0.001 |
| 4. Pantobiol-4-120 mg/kg | 16.3±3.9 | 12.8±5.6 | 4.5±2.2 | 8.3±3.8 | 32.8±21.0<br>* p=0.029<br># p=0.013 |
| 5. Pantobiol-4-2 45 mg/kg | 16.0±5.6 | 10.8±6.7 | 3.7±2.5 | 7.1±4.5 | 35.9±20.9<br>* p=0.0033<br># p=0.002 |
| 6. Pantobiol-4-2 20 mg/kg. | 16.2±3.9 | 10.7±5.0 | 2.9±2.2<br># p=0.02 | 7.8±3.2 | 52.1±21.0<br># p<0.001 |
| 7. Pantobiol-4-3 45 mg/kg | 15.9±4.7 | 13.3±4.7 | 3.8±1.7<br># p=0.03 | 9.5±3.5 | 46.8±20.9<br># p<0.001 |
| 8. Pantobiol-4-3 20 mg/kg | 15.6±5.0 | 11.3±3.7 | 3.1±1.7<br># p=0.02 | 8.2±2.4 | 42.6±20.8<br># p<0.001 |

* The significance level of differences from sham-operated animals (Tukey HSD criterion), # The significance level of differences from the control group (Tukey HSD criterion)

Statistical analysis (ANOVA) showed that the group factor significantly influenced total exploration time ($p = 0.018$). Post-

hoc tests revealed that rats treated with 45 mg/kg of Pantobiol 4-1 spent less time exploring objects than sham-operated animals, though they did not differ significantly from the AD-control group.

To quantify long-term memory retention, we primarily relied on the Recognition Index (RI). Our findings confirmed the validity of the AD model, as evidenced by a substantial decline in RI scores within the control group. In contrast, groups 3-8 showed improved RI values mainly because they spent less time re-exploring "familiar" objects, indicating better memory retention. Notably, Pantobiol 4-3 exhibited the most consistent restorative effect, showing no significant difference from the healthy sham-operated group.

*Passive Avoidance Test*

During the preliminary stage of training, all experimental cohorts displayed uniform motor activity and light-avoidance behavior, with no statistically significant variance ($p = 0.86$). However, in testing sessions, the AD-control group and the high-dose Pantobiol 4-1 group (Group 3) showed significantly shorter latencies compared to sham rats. Conversely, Groups 4-8 demonstrated a marked increase in latency, suggesting the successful restoration of learning capacity **(Table 2)**.

**Table 2.** Study on the effects of dietary supplements on learning indicators in passive avoidance models in rats with beta-amyloid introduction

| Animal Groups | Time of transition to the dark compartment during a training session, s | Time of transition to the dark compartment during a testing session, sec | Increased time of transition to the dark compartment during a testing session compared to the training session, sec |
|---|---|---|---|
| 1. False operation | 16.6±12.0 | 149.0±43.5<br># p< 0.001 | 132.1±42.2<br># p<0.001 |
| 2. Control | 19.9±15.6 | 66.4±60.7<br>* p< 0.001 | 46.5±50.6<br>* p< 0.001 |
| 3. Pantobiol-4-1 | 18.0±17.0 | 95.2±44.2<br>* p=0.004 | 77.2±45.7<br>* p=0.048 |
| 4. Pantobiol-4-1 | 24.9±18.8 | 128.0±29.0<br># p=0.001 | 103.1±26.2<br># p=0.005 |
| 5. Pantobiol-4-2 | 27.2±23.5 | 160.3±25.7<br># p< 0.001 | 133.1±33.5<br># p< 0.001 |
| 6. Pantobiol-4-2 | 21.4±21.7 | 144.0±40.4<br># p< 0.001 | 123.6±44.7<br># p< 0.001 |
| 7. Pantobiol-4-3 | 25.1±27.0 | 157.2±27.8<br># p< 0.001 | 132.1±47.9<br># p< 0.001 |
| 8. Pantobiol-4-3 | 17.1±8.9 | 140.5±42.5<br># p< 0.001 | 122.6±40.6<br># p< 0.001 |

* The significance level of differences from sham-operated animals (Tukey HSD criterion), # The significance level of differences from the control group (Tukey HSD criterion)

*Cholinergic and Hormonal Status*

As anticipated, the AD-control group exhibited a sharp decline in ChAT activity. Treatment with Pantobiol 4-2 and 4-3 (20 mg/kg) effectively brought ChAT activity back to levels comparable to the sham-operated group **(Table 3)**, confirming a neuroprotective effect on cholinergic neurons.

**Table 3.** Choline acetyltransferase (ChAT) activity in the rat brain nucleus

| Group | ChAT activity (nmol ACh per 1 mg of tissue per 1 minute) |
|---|---|
| Sham operation | 23.71±4.3 |
| Control (Beta-amyloid 25-35 to the nucleus of Meynert + water) | 15.91 ±3.0** |
| Beta-amyloid 25-35 to the nucleus of Meynert + Pantobiol 4-2 at a dose of 20 mg/kg | 22.38±3.4^^ |
| Beta-amyloid 25-35 to the nucleus of Meynert + Pantobiol 4-3 at a dose of 20 mg/kg | 21.63±3.1^^ |

*The significance level of differences from sham-operated animals (Tukey HSD criterion), ^^The significance level of differences from the control group (Tukey HSD criterion)

Pantobiol 4-2 and 4-3 administration dramatically increased testosterone levels, although amyloid injection alone did not change them, according to serum analysis. Interestingly, DHEA levels rose in response to amyloid-induced stress; however, the

administration of the biocomplex at 45 mg/kg normalized these levels to baseline, suggesting an anti-stress and antioxidant effect **(Table 4)**.

**Table 4.** Levels of testosterone and DHEA in blood plasma in animals of different groups

| Animal Groups | Testosterone (nm /L) | DHEA (ng /ml) |
|---|---|---|
| 1. Sham operation | 13.0±4.8 | 0.37 ±0.03<br># p< 0.001 |
| 2. Control | 14.0 ±3.5 | 0.57 ±0.03<br>*p< 0.001 |
| 3. Pantobiolum-4-1 45 mg/kg 1 | 18.0±4.5<br>* p< 0.05<br>#p=0.052 | 0.38 ±0.05<br># p< 0.001 |
| 4. Pantobiol-4-1 20 mg/kg | 15.4±2.8<br>*p>0.1<br>#p>0,1 | 0.47 ±0.04<br># p=0.001<br>* p< 0.001 |
| 5. Pantobiolum-4-2 45 mg/kg 2 | 28.6 ±7.9<br>* p< 0.01<br># p< 0.01 | 0.39 ±0.05<br># p< 0.001 |
| 6. Pantobiol-4-2 20 mg/kg | 23.2 ±4.50<br>* p< 0.01<br># p< 0.01 | 0, 46 ±0,03<br># p< 0.001<br>* p< 0.001 |
| 7. Pantobiol-4-3 45 mg/kg | 22.5 ±3.14<br>* p< 0.05<br>#p=0.052 | 0.38 ± 0.02<br># p< 0.001 |
| 8. Pantobiol-4-3 20 mg/kg 2 | 20.2±2.7<br>* p< 0.05<br>#p=0.052 | 0.43±0.03<br># p< 0.001<br>* p< 0.001 |

*The significance level of differences from sham-operated animals (Tukey HSD criterion), #The significance level of differences from the control group (Tukey HSD criterion)

It should be noted that the testosterone level in Group 5, which received 45 mg/kg Pantobiol-2, was significantly higher (p< 0.05) than in the groups receiving the dietary supplement.

The introduction of beta-amyloid increased the DHEA level in the blood serum. The biocomplex in the amount of 45 mg/kg reduced the hormone level to the level observed in sham-operated animals. None of the drugs at a dose of 20 mg/kg affected the DHEA level.

## Conclusion

Research indicates that Pantobiol-4 biocomplexes effectively mitigate the neurotoxic damage caused by beta-amyloid in the basal nuclei. The data suggest that Pantobiol 4-3 offers the most balanced therapeutic profile for cognitive recovery. The inverse dose-dependent relationship observed in some formulations suggests a complex interaction between hormonal stimulation and neuroprotection. Ultimately, these biocomplexes serve as potent agents for stabilizing CNS function and preventing the biochemical degradation associated with Alzheimer's disease.

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