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Preclinical Research Optimization of Medicinal Products with Action of the Inner Ear

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For all types of drugs and clinical trials in the drug development process, the use of non-clinical models and relevant animal species is essential to obtain predictive data for humans. Sensorineural hearing loss is a condition that manifests clinically through perceptual hearing impairment. Fixed-dose combinations have advanced in many therapeutic areas, including inner ear pathology, where hearing disorders and balance are increasingly prevalent. Within the Scientific Center of Medicines, a fixed-dose combinations medicinal product was developed with potential efficacy in the treatment of vestibulo-cochlear disorders. This product containing capsules of Nicergoline, Piracetam, and Hawthorn Extract.

The presented national project (no. 20.80012.8007.02SE, 2024-25) proposes streamlining preclinical research methods for medicinal products acting on the auditory and vestibular system in accordance with current requirements of experimental modeling for laboratory animals. All procedures describing experiments involving laboratory animals were conducted in accordance with Directive 2010/63/EU and national Law no. 211/2017. The research algorithm consists of: establishing the method for inducing sensorineural hearing loss and peripheral vestibulopathy; experimental audiometric methods (otoacoustic emissions, Preyer reflex) for monitoring sensorineural hearing loss; preclinical testing of static and dynamic locomotor coordination in Wistar rats (open field test, horizontal walking, and forced motor activity test to maintain balance).

Preclinical research in the fields of audiology and experimental vestibulometry demonstrated the beneficial effect of the studied product in the complex treatment of sensorineural hearing loss and peripheral vestibular disorders. The combination therapy yielded the most significant benefits, with no notable side effects observed. Considering the complex etiology and multifactorial pathophysiology of these conditions, the development of combination therapies is of growing interest.

Has been developed a practical basis for an interdisciplinary and systemic conceptual approach of preclinical studies on the development, pharmacological treatment of sensorineural hearing loss and vestibulopathy. The expected result of the study is the development of a new methods and optimizing existing methods for experimental modeling of inner ear diseases and balance disorders. The novelty of the project involves measuring the effectiveness audiometric and vestibulometric preclinical researches of sensorineural hearing loss and peripheral vestibulopaty.

Keywords: otoacoustic emissions, fixed-dose combined medicinal product, preclinical research, sensorineural hearing loss, vestibular disorders

Introduction

Scientific research on animals, although it presents a difficult ethical dilemma, is currently still indispensable for biomedicine, contributing too many medical advances that improve human health. The role of laboratory animals continues to be crucial in understanding the fundamental processes of life and in developing new treatments (Festing et al., 2002). In the future, despite the ongoing efforts to find alternative methods to animal research, there will likely remain areas of fundamental or behavioral research that cannot be fully replaced. At the same time, it is equally necessary and important for society to be aware of the latest developments and medical innovations that do not involve the use of animals, but are scientifically tested and validated (Festing et al., 2002; Liu et al., 2013).

For all types of drugs and clinical trials in the drug development process, the use of non-clinical models and relevant animal species is essential to obtain predictive data for humans (Sawicki-Wrzask et al., 2015). Sensorineural hearing loss is a condition that manifests clinically through perceptual hearing impairment. Sensorineural Hearing Loss (SHL) affects the perception of sounds from the inner ear, auditory nerve, subcortical, and cortical auditory centers. The drug treatment of

SHL is usually symptomatic and includes vasodilators, steroids, nootropics, and antioxidants (Mukherjea et al., 2011). Given the complex etiology and multifactorial pathophysiology of SHL, the development of combination therapies is gaining increased attention. An imbalance between lipid peroxidation processes and the antioxidant defense system has been demonstrated in liver diseases such as chronic hepatitis and hepatic cirrhosis (Mukherjea et al., 2011). At the Drug Development Center of the Nicolae Testemițanu State University of Medicine and Pharmacy, two new combined drugs in capsule form are currently under development. These formulations contain the following active pharmaceutical ingredients: arginine aspartate, ornithine aspartate, and resveratrol (Parii et al., 2025). Fixed-dose combinations have advanced in many therapeutic areas, including inner ear pathology, where hearing disorders and balance are increasingly prevalent.

Materials and Methods

Within the Scientific Center of Medicines, a fixed-dose combination medicinal product was developed with potential efficacy in the treatment of vestibulo-cochlear disorders. This product containing capsules of Nicergoline, Piracetam, and Hawthorn Extract (Rus et al., 2025).

The presented national project (no. 20.80012.8007.02SE, 2024-25) proposes streamlining preclinical research methods for medicinal products acting on the auditory and vestibular system in accordance with current requirements of experimental modeling for laboratory animals (Parii et al., 2025). Pharmaceutical analysis employed chemical methods (UV-VIS spectrophotometry) and chromatographic techniques (HPLC and GC) (Rus et al., 2025; Uncu et al., 2021). All procedures describing experiments involving laboratory animals were conducted in accordance with Directive 2010/63/EU and national Law no. 211/2017 (European Union, (n.d.)). The research algorithm consists of: establishing the method for inducing sensorineural hearing loss and peripheral vestibulopathy (Parii et al., 2025); experimental audiometric methods (otoacoustic emissions tipe TEOEA and DPOEA, Preyer reflex) for monitoring sensorineural hearing loss; preclinical testing of static and dynamic locomotor coordination in 40 Wistar rats (open field test, horizontal walking, and forced motor activity test to maintain balance). According to the activity plan, the SOP "Examination of the auditory and vestibular apparatus in rats" was developed (Parii et al., 2025; Rus et al., 2025; Hong et al., 2006).

The following activities were carried out: development of the protocol for functional examination in laboratory animals; development, submission of the file and obtaining a positive opinion from the institutional Research Ethics Committee (no.7, 21.10.2024).

Results and Discussion

The production technology for the experimental series of the medicinal products has been established. Chemical and pharmaceutical studies demonstrated the compatibility of the active ingredients and excipients in the formulations of elaborated medicinal product. The expected result of the study is the development of a new methods and optimizing existing methods for experimental modeling of inner ear diseases and balance disorders.

Pharmacological investigations, carried out in accordance with *OECD TG 423* (*Acute Toxic Class Method*) guidelines (Organisation for Economic Co-operation and Development (OECD), 2002), indicated minimal toxicity — corresponding to toxicity class 5 (LD_{50} > 5000 mg/kg) at product with contain arginine aspartate, ornithine aspartate, and resveratrol. The obtained data provide a foundation for continuing pharmaceutical and preclinical pharmacological research to further evaluate the efficacy and safety of the developed products.

In gentamicin-induced SHL models, animals treated with the test product showed a clear otoprotective effect. Audio logical tests (Fig. 1) evidenced by improved optoacoustic emission results TEOAE, DPOAE > 0 dB SPL; signal-to-noise ratio > 3 dB SPL in the 1000–4000 Hz range, in contrast to the untreated ototoxicity group ($p < 0.05$). Vestibular testing (horizontal walking with Cat Walk, and forced motor activity test to maintain balance) confirmed the efficacy of the test product, with the greatest therapeutic benefits observed in the treated group and no significant side effects noted (Fig. 2, 3).

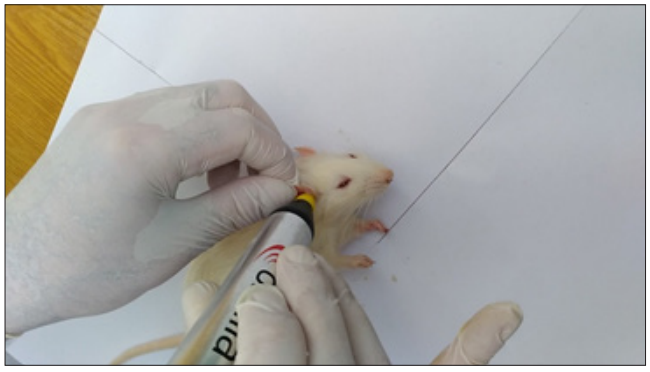

Figure 1: Ear analyser in rats

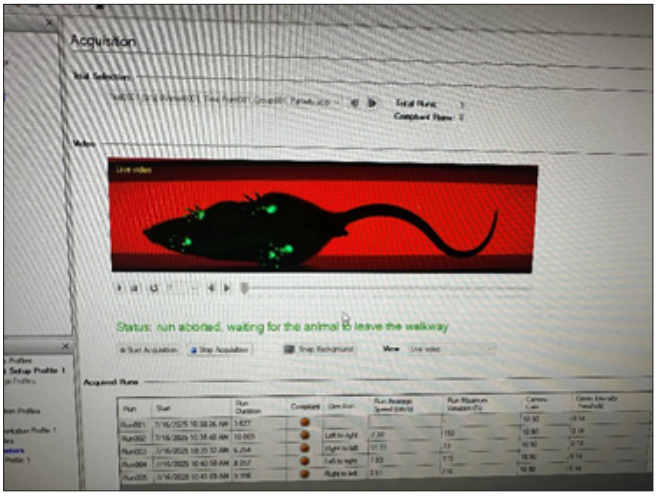

Figure 2: Balance tests with Cat Walk

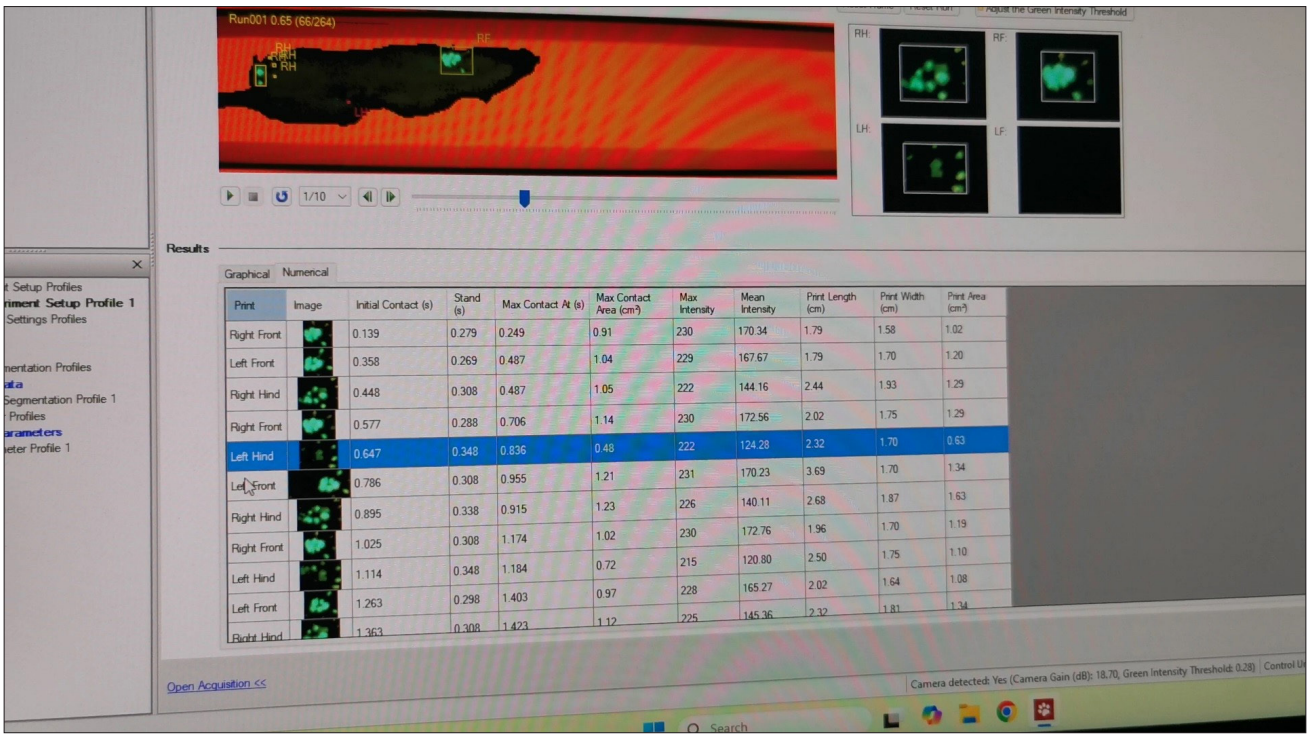

Figure 3: Balance Analyser

Preclinical research in the fields of audiology and experimental vestibulometry demonstrated the beneficial effect of the studied product in the complex treatment of sensorineural hearing loss and peripheral vestibular disorders. The combination therapy yielded the most significant benefits, with no notable side effects observed. Considering the complex etiology and multifactorial pathophysiology of these conditions, the development of combination therapies is of growing interest.

The results were implemented in the practical activities of the "Nicolae Testemitanu" State University of Medicine and Pharmacy. The project was mentioned with a Bronze Medal and Special Award Certificate offered by Inventcor at the Euroinvent 2025 International Specialized Exhibition, Romania (Parii et al., 2025).

One of the most debated topics in the field of biomedical research, animal testing has raised many moral and ethical issues over the past two centuries. In recent history and currently, preclinical research is based on the 3Rs principle: Replacement, Reduction, and Refinement. The progress made over the past two decades in research aimed at finding and applying alternatives to the use of animals (especially mammals) must be acknowledged and recognized by society. Today, collaborations between governmental organizations, academia, and the private sector have materialized through innovative programs that help accelerate the transition toward "animal-free" technologies in research.

Has been developed a practical basis for an interdisciplinary and systemic conceptual approach of preclinical studies on the development, pharmacological treatment of sensorineural hearing loss and vestibulopathy. The expected result of the study is the development of a new methods and optimizing existing methods for experimental modeling of inner ear diseases and balance disorders. The novelty of the project involves measuring the effectiveness audiometric and vestibulometric preclinical researches of sensorineural hearing loss and peripheral vestibulopaty.

Conclusions

- This study pharmacologic characterized a novel combined drug in capsules containing nicergoline, piracetam, and hawthorn extract, for potential use in SHL therapy.
- The data of experimental audio logical and vestibular tests in rats encouraging further preclinical and clinical research.
- In medical practice, the elaboration and use of the multicomponent preparations, containing synthesis and naturist substances is a perspective direction for the treatment of sensorineural disorders.
- A theoretical and practical basis was developed for an interdisciplinary and systemic conceptual approach to preclinical studies on the pharmacotherapy of cochleo-vestibulopathies with potential for further development of the topic within national and international research projects.

Acknowledgement

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