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Reptiles as Experimental Models: Uncovering Their Role in Drug Development and Health Research

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Experimental animal models are indispensable as they help to enhance the understanding of unknown diseases and contribute to new discoveries through their physiology, which facilitates the learning process and scientific dissemination. Consequently, the techniques applied to animal models require the development of guidelines that ensure respect for these animals and the reliability of the results obtained, in order to promote the advancement of scientific progress. With this in mind, the aim of the present study was to conduct a review on the use of reptiles as experimental models. The works were reviewed and selected based on their use of animals (reptiles) as experimental models and for having results relevant to the development of science and its various applications. In this context, analyzes that adhered to these principles were also considered, revealing that certain species of snakes, lizards, and turtles show promise for research in pharmaceuticals, the production of medicines and vaccines, as well as in seeking solutions to other problems related to animal health, for example, the study of baseline corticosterone (CORT) concentrations in rattlesnakes. Thus, we can conclude that, although these animals are not as commonly used in experimental research, reptiles hold an important position among vertebrates for investigating the progression of serious diseases, as well as for the development of vaccines and medications.

Keywords: Illnesses; search; animal health; reptiles.

1. INTRODUCTION

Experimental models aim to enhance knowledge about diseases and treatments, playing a fundamental role in evaluation, monitoring, and sometimes even in curing conditions. To develop these studies, it is necessary to decide on the method that will be employed to verify the hypotheses proposed by scientists. Indeed, it is important to remember that experimental models also assist in understanding natural phenomena, as well as broadening physiological knowledge, the etiopathogenesis of diseases, drug actions, surgical outcomes, and interventions, ultimately helping to confirm isolated hypotheses in humans due to certain biological variables (Watanabe et al., 2014; Taylor et al., 2021).

Thus, understanding the main classifications of experimental models in research is essential for the refinement and validation of existing techniques and procedures, as well as for the development of new ones. Experimental models and research represent simplifications of recent or past events, materializing a portion of reality. They are effective when demonstrated accurately through prior validation and by recognizing the limitations relative to the reality they represent (Ferreira et al., 2005). The greater the uniformity of the animals in relation to environmental, genetic, and experimental variables, the smaller the minimum sample size required for the research to be conducted (Ferreira et al., 2005). Another important aspect of these models is the emphasis on the necessity to uphold ethical standards and avoid primary interventions, particularly in humans. Therefore, experimental models should resemble the object of study as closely as possible (Ferreira et al., 2005).

There are several types of experimental models used in scientific research, such as the use of animals, known as in vivo models, and the use of immortalized cells, referred to as in vitro models (Watanabe et al., 2014). To better understand experimental models in in vivo research, they are categorized into four groups, according to the experimentation model, to better differentiate types of potential diseases: induced—situations where the disease to be investigated must be experimentally induced; spontaneous—genetic variations of human diseases that may result in a specific disease or that do not exhibit a reaction to a specific stimulus; naturally occurring in animals; and negative—using animals that do not develop the disease being studied, and orphan—a natural condition in animals that was not initially described in humans but is adopted after diseases are identified in them (Watanabe et al., 2014).

Animal experiments are prominent in health research, particularly in the treatment of myocardial diseases, cancer, diabetes, chronic-degenerative diseases, and the development of vaccines, which we have recently witnessed rapid progress. Advances in pharmacology and healthcare practices often stem from animal models. However, for these experiments to develop successfully, it is essential to adopt

humane care practices for research animals and ensure strategies are in place to promote animal welfare (Watanabe et al., 2014).

In this summary, we will review bibliographic studies on how reptiles can be used to find answers to incurable diseases, more efficient treatments, vaccines, medications, and other advancements that demonstrate the scientific potential of these animals (Achim, 2007; Poletta et al., 2013; Maceda-Veiga et al., 2015). For example, reptiles hold an important position among vertebrates for investigating the evolution of modulatory mechanisms in the cardiovascular system. This work evaluates the effectiveness of a new experimental model for cardiovascular studies in Squamata, using decerebrated animals. The model allows for the recording of various physiological variables in an euthanized animal preparation with a functional autonomic nervous system (ANS), free from anesthetic interference (Tavares, 2021).

In an experiment involving juvenile and adult turtles of the species *Kinosternon scorpioide*, the animals were subjected to fasting and later refeeding to observe metabolic changes in the blood caused by food deprivation and refeeding, as well as differences in glycogen and total lipid concentrations in the liver and muscle after fasting and refeeding (Oliveira, 2010). These studies are examples of how these animals play a significant role in the treatment of diseases, the development of medications and vaccines, and potentially even the cure for more severe illnesses. Throughout this work, we examine in a discursive manner how this model functions and its benefits for various research fields.

2. METHODOLOGY

A comprehensive bibliographic review, of a narrative type, was conducted using databases such as Science Direct, academic university repositories, and scientific journals in the field. The research was carried out over eight stages, defined as: defining the research question; conducting a broad bibliographic search; selecting relevant studies; qualitative evaluation of the selected studies; analysis and synthesis of the data obtained; interpretation of the results; reporting and presentation of these results; and periodic updating of the review. The review was based on four inclusion criteria: original works in Portuguese and English, published between 2019 and 2024, and fully available in the selected scientific databases. The following descriptors were used: (experimental models) OR (modelos experimentais) AND (research) OR (pesquisa) AND (reptiles) OR (répteis).

3. RESULTS AND DISCUSSION

The discussion highlights various reptile species and their physiological characteristics, demonstrating a solid understanding of comparative biology and supporting their use as experimental models for human health. Experimental models involving animals provide opportunities to understand their physiology, the etiopathogenesis of diseases, and the actions of medications related to their health. In this context, the studies reviewed report principles associated with ethical procedures aimed at ensuring animal welfare and their use in scientific health research. Consequently, the techniques and behaviors applied to animal models necessitate the development of guidelines that ensure respect for the animals and the reliability of the results obtained, in order to enhance the progress of scientific advancement.

Therefore, the study of animals as experimental models, specifically reptiles, is essential due to the lack of research encompassing this group, which can facilitate various applications for both animal and human health. Mammals are the most commonly used in research, however, reptiles offer advantages such as metabolic adaptability, insights into disease mechanisms, and regenerative medicine, making them a highly effective experimental model. In addition, it is important to highlight the ethical principles involved in following the Three Rs rule: reduction, replacement, and refinement, which emphasizes that the priority of experimental research with animals is their welfare, aiming to minimize suffering or stress whenever possible. Ultimately, these unquestionable contributions link scientific research and the advancement of science as fundamental aspects for ethical procedures involving animals. Six studies were selected that support the investigation of reptiles as experimental models, providing various applications for health according to their categories.

In the study by Tylan et al. (2020), the authors highlighted the efficiency of measuring baseline corticosterone (CORT) concentrations in four reptile species, including rattlesnakes (*Crotalus oreganus*), using their blood plasma. Their

Table 1. Procedures and/or medications used in reptiles

Species	Procedure and/or Medication	Reference
Eastern Box Turtles	Ketorolac	(Cerreta et al., 2019)
Western Rattlesnakes (Crotalus oreganus)	Plasma Collection	(Tylan et al., 2020)
Royal Pythons	Alfaxalone-Midazolam and Dexmedetomidine-Midazolam	(Yaw et al., 2020)
Gecko	Analysis of Astrocytes	(Du et al., 2021)
South American Rattlesnakes (Crotalus durissus)	Cardiovascular Adjustments	(Tavares, 2021)
House Geckos (Hemidactylus flaviviridis)	Nefastin-1	(Dotania et al., 2023)

findings suggested that plasma samples collected between 2 and 3 minutes likely approximate baseline CORT concentrations, although this may be overly conservative for some reptile species. Nonetheless, it is important to note that they compared CORT concentrations in blood samples collected after a significant change was observed, specifically following the animals' exposure to a stress protocol. Thus, a hypothesis arises that, due to the lower metabolic rates of reptiles compared to other avian species previously tested, there were greater delays in the increase of plasma CORT concentrations resulting from standard stress exposure.

In another analysis, the study proposed by Dotania et al. (2023) reports on the role of nefastin-1 in reptiles, particularly its hormonal function in the testes of house geckos. Nefastin-1 is a pleiotropic hormone implicated in various physiological functions, including reproduction. However, there are limited studies that have established the essential role of this peptide in regulating testicular functions in mammals and fish. The role of this hormone in the homeostasis of spermatogenesis and testicular steroidogenesis remains unexplored in reptiles. Therefore, this study aimed to provide insights into testicular function during the reproductive phase.

In this context, the expression of nefastin-1 in the testes of house geckos varied significantly depending on the reproductive phase, being higher during the active phase and lower during the regressive phase. Furthermore, the hormone stimulated an anti-apoptotic marker while inhibiting another, suggesting a role as an inhibitor of testicular cell apoptosis. Consequently, the treatment of house gecko testes with nefastin-1 demonstrated an effective outcome that depended on the concentration and duration of the peptide, correlating with an increase in testosterone production by the testes, thereby indicating a hormonal regulation.

4. CONCLUSION

Given the results from the studies to be presented, it is evident that the use of reptile species as experimental models can be promising for drug development and clinical trial testing. However, in the future, more in-depth studies are necessary to evaluate the efficacy of some of the medications and procedures discussed in the research, utilizing more precise assessment tools, such as nociceptive assays, instead of relying solely on observational evaluations of the clinical progression.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc. have been used during the writing or editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology.

Details of the AI usage are given below:

1. The generative AI technology used was ChatGPT, which is based on large language models (LLMs) developed by OpenAI. The applied version is the most recent in the series, belonging to the GPT-4 (Generative

Pre-trained Transformer 4) family. All of the generative artificial intelligence behind ChatGPT was developed and trained by OpenAI.

2. The technology was used strictly to assist in the translation of the manuscript from Brazilian Portuguese to English for the purpose of publication in the current journal. After the translation, the text was reviewed again by team members to identify and correct any potential translation errors.
3. The input prompt used was: "Translate the text from Portuguese to English, without altering the meaning of the sentences."

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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