ABSTRACT

Fundamental pharmacological research was and will be the milestone for evaluating drug efficacy and safety, including drugs already registered and used in therapy. Among the advantages of preclinical studies are that the experiments can be repeated if re-evaluations of the experimental protocol are necessary, they can use enough animals for the results to have statistical power, respectively they allow the harvesting of biological tissue samples for histopathological evaluation or immunohistochemistry. Another important aspect in pharmacological research is the development of analytical methods for the determination of active substances or metabolites in various biological samples as well as biochemical markers necessary for the evaluation of the safety profile of substances.

The habilitation thesis follows three important research directions:

Part I - Fundamental Pharmacological Research

*I.1 Animal models for evaluating the efficacy and safety of pharmacotherapy***.**

A detailed understanding of the impact and complex interactions between drugs and living systems is crucial, with the ultimate purpose to test the drug in clinical trials, on human subjects, these trials being approved only for substances for which the pharmacological profile is known in as much detail as possible.

This thesis presents three animal models that were used in therapeutic efficacy studies, both for pharmacologically active substances and for phytotherapeutic extracts, namely:

1. Animal doping model with androgens, used to evaluate the benefit of using aromatase inhibitors as adjuvant therapy to anabolic steroids. The study follows the effects of combined therapy (testosterone and letrozole) on the integrity of the hypothalamic-pituitary-testicular axis, on sperm characteristics, as well as on prospective and copulatory behavior.

2. Animal model of drug-induced pseudoparkinsonism by haloperidol. The model was used to evaluate the potential use of metformin to reduce the extrapyramidal side effects of antipsychotics with increased affinity for dopamine D_2 receptors.

3. Animal model of type 1 diabetes induced by streptozotocin, used to evaluate the therapeutic effects of some phytotherapeutic extracts. The model was used to evaluate the modifications of biochemical parameters and the evolution of complications in individuals with type 1 diabetes induced by blueberry extracts (*Vaccinium mythilus*). The same animal model was used to test the influence of *Tribullus terestris* extracts on biochemical parameters and vascular complications (erectile dysfunction) in diabetes.

I.2 Preclinical studies of pharmacological safety

Drug safety studies aim to evaluate the toxic potential of a drug in humans or experimental animals. Even if these tests are performed early in the testing protocol of a new drug, it is possible that certain toxic effects may not be identified until later studies.
Since the safety of antipsychotics is still not completely known and the scientific literature is still controversial regarding their pharmacotoxicological profile resulting from different affinity for several receptor subtypes, this thesis presents safety-studies for olanzapine, risperidone and amisulpride. The experiments focused on establishing how they influence body weight, different biochemical parameters (glycemia, ALT, AST, total cholesterol, triglycerides, as appropriate), respectively on how they affect the morphological integrity of different organs (adipose tissue, liver, as appropriate).

I.3 Analytical methods for quantifying active substances/ metabolites from biological samples

Analytical methods are essential to accurately determine the concentration of the active substance or metabolites in various biological samples. This is necessary both for establishing the pharmacokinetic profile of the substance and for the correct evaluation of therapeutic and/or toxic effects in direct correlation with the concentration of the active substance at the tissue or organ level.

Present thesis presents two analytical methods developed for efficacy and safety studies, specifically a method for testosterone/dihydrotestosterone, respectively of amiodarone/desethylamiodarone quantification.

Part II - Oxidative stress, between benefit and risk

Oxidative stress is defined as an imbalance between the production of reactive species (oxygen and nitrogen) and the ability of the extracellular and intracellular protection systems to neutralize them. Substances with tropism on the central nervous system, such as caffeine or cannabidiol, are supposed to have beneficial effects in neurodegenerative diseases due to their antioxidant potential. In this section, the possible mechanisms by which they could favorably influence the evolution of neurodegenerative pathologies are analyzed and presents the analytical methods developed to quantify the oxidative status (the method for determining malondialdehyde, respectively the method for evaluating the ratio of reduced glutathione/oxidized glutathione) from biological samples.

Part III - Drug therapy from the physician/patient perspective

To establish preventive measures to avoid the abusive use of drugs, it is necessary to evaluate the patients' perception in the form of questionnaires and depending on the answer, the need to implement information campaigns on the benefits/risks of using certain drug

classes can be initiated. Questionnaire-based studies can also be used to evaluate the effectiveness of therapy.

In this thesis, the purpose of the questionnaire-based studies was:

1. The attitude of young women regarding the use of hormonal contraception according to religious affiliation and the degree of knowledge regarding their safety profile.

2. The effectiveness of antidepressant treatment in combating somatic and psychological manifestations associated with stressful situations such as the COVID-19 pandemic.

3. Management of upper respiratory tract infections from the perspective of parents/legal guardians.