UNIVERSITY OF MEDICINE AND PHARMACY „IULIU HATIEGANU" CLUJ-NAPOCA

Habilitation thesis

The efficacy and safety of medicinal substances or with medicinal potential, assessed in preclinical and clinical studies

ABSTRACT

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The habilitation thesis entitled "Efficacy and safety of medicinal substances or with medicinal potential, assessed in preclinical and clinical studies" summarizes the scientific professional and academic research, conducted after PhD defense in 2001. The doctoral thesis, carried out under the coordination of Academician Prof. Dumitru Dobrescu, PhD, entitled "Experimental pharmacological research on some plant products with anti-inflammatory activity", permitted the development of current and future research directions. The research directions discussed were based on experimental models developed and validated within the thesis. Moreover, they were enriched with new directions in preclinical and clinical field. The results of scientific research were structured according to the established objectives.

The first objective was to assess the anti-inflammatory and analgesic efficacy of vegetable products and synthetic substances. Models of acute inflammation were used to test vegetable products extracted from different plant species, including: *Calluna vulgaris, Onopordon acanthium, Achillea millefolium* and *Achillea distans, Solanum villosum, Peucedanum officinale, Nigella Damascena* and *Nigella sativa, Melampyrum bihariense* and *Melampyrum cristatum, Thymus pulegioides, Ruscus aculeatus*. The same models were also used to study the anti-inflammatory potential for synthetic compounds, some of them being the objective of research projects won by competition. Therefore, the anti-inflammatory effect of the following compounds were analyzed: p-toluenesulfonyl-hydrazino-thiazole, 5-(pyridin-4-yl)-1,3,4-oxadiazole-2-thiol, 5-(pyridin-4-yl)-1,3,4-thiadiazole-2-thiol and 5-(pyridin-4-yl)-1,2,4-triazole-3-thiol, thiazolyl-mercaptotriazole, and their precursors (thiosemicarbazones-thiazolyl, thiazolyl-carboniltiosemicarbazide) as well as of thiazolo-triazoles and pyrazoles obtained by the thiazolyl-mercaptotriazoles pathway, Schiff bases, Mannich polyheterocycle bases and novel compounds pyridyl-thiazolo[3,2-b][1,2,4]triazoles.

Pain is a symptom accompanying inflammation, but which can also may occur independently of it. Pain can be induced by thermal, mechanical or chemical stimuli. Analgesic substances or with analgesic potential, having central and/or peripheral mechanisms of action, were assessed in different models for the study of pain. Nowadays, the use of analgesics in clinical practice is an issue of interest for all healthcare professionals. Studies have been conducted on the use of analgesics for the treatment of postoperative pain, for cancer pain treatment and regarding their dispensing patterns in community pharmacy.

The second objective was to assess the diuretic, saluretic and uricosuric effect of some vegetable products obtained from species such as: *Adonis aestivalis, Anthemis tinctoria, Pulmonaria officinalis, Melampyrum bihariense* and *Melampyrum cristatum, Betula verrucosa* and *Fraxinus excelsior, Syringa vulgaris , Orthosiphon stamineus, Calluna vulgaris, Phyllitis scolopendrium, Solidago virgaurea, Ononis spinosa, Nigella sativa* and *Nigella damascena, Hieracium pilosella,* species of the genus *Epilobium, Stereospermum kunthianum.*

A third objective was to conduct physiological and pharmacological studies on isolated organs, the method being implemented due to a Tempus scholarship in 1994 at ULB Brussels. Some of the isolated organ studies were carried out as student researches and others by working under a research grant obtained through competition.

The fourth objective was to evaluate the antioxidant potential of some vegetable or synthetic compounds, mainly of alpha-lipoic acid and vitamin E, in different experimental models in which oxidative stress was induced.

The fifth objective was to study the pathophysiological and pharmacological characteristics of cardiovascular diseases such as heart failure and dilated cardiomyopathy, and of metabolic syndrome. Experimental models of heart failure and metabolic syndrome were developed in order to test different medicinal substances or with medicinal potential. Important biomarkers were highlighted to characterize the diseases and their evolution, and at the same time clinical therapeutic aspects were assessed, especially in the case of dilated cardiomyopathy.

The sixth objective was the study of medicines' safety issues, both preclinical and clinical. Pharmacovigilance activity was developed at the Drug Research Information Centre, part of our university, through the three projects conducted, of which one was international. Drug safety issues were determined in clinical or pharmaceutical practice. Many of the adverse drug reactions identified were assessed as avoidable, one of the causes being the presence of drug-drug interactions. A series of studies identifying, characterizing and evaluating the consequences of drug-drug interactions were developed both in clinical practice and in community pharmacy. Following the experience acquired by the work group, the first pharmacovigilance book after 1989 was written and entitled "Introduction to Pharmacovigilance". Also, each trimester, a pharmacovigilance bulletin is being elaborated and made available online for healthcare professionals.

Teaching activity is complex and it consists mainly of courses activities at undergraduate, master and residency level. Besides Pharmacology courses for third and fourth year Pharmacy students, I conducted general Anatomy-Physiology and Pathophysiology courses, both for the Romanian and French line students. Since 2013, I proposed and now successfully I am conducting a Master Program entitled "Pharmacovigilance- drug safety monitoring". Alongside, I conduct teaching activities with residents of Clinical Pharmacy and Pharmaceutical Laboratory specialties. The teaching activity is fulfilled by the coordination of 104 Diploma Thesis and 6 Dissertation Thesis, and the publication of 13 personal or collaboration scientific volumes addressing pharmacy students and pharmacists.

In the future, research will be continued and developed on the same directions, and at the same time, our aim is to implement new experimental methods that can allow a more complex analysis of certain diseases and drug therapies through specific molecular parameters. In order to access new research projects and to enable increased visibility of our research, an important role will have new collaborations in the country and abroad. Regarding teaching activity, it will be centered on students and the needs of pharmacist profession. Thereby, the graduate can have the knowledge and qualifications necessary for rapid integration into the labor market, taking also into consideration the various opportunities and performances required by each job.