

## Abstract

This habilitation thesis (titled “Multiple approaches and perspectives in the assessment of safety and efficacy of medicinal products”) is based on my research and professional activities performed after the defense of my PhD thesis titled “Correlations between the metabolism of *Cuscuta* indigenous species and their hosts, with a view of establishing the species with the highest cytostatic potential” (prof. Viorica Istudor, PhD, was my doctoral advisor).

The thesis is structured in 3 parts. By far the largest, the first one (Scientific activity) deals with the main directions of my scientific research: (1) Safety assessment of medicines by a variety of approaches, mostly non-conventional. (2). Non-clinical assessment of the efficacy of medicinal products and discovery of new medicinal products or other healthcare productst, and (3) Other scientific publications, a short subsection illustrating the diversity of my scientific preoccupations, without being exhaustive.

For the safety assessment of natural or synthetic medicinal products (the first subsection of the first part), we have used a variety of approaches: a) phytotoxiciy assessment on Monocot and Dicot herbal species, for both herbal extracts and chemical substances; b) acute toxicity using *Artemia franciscana* Kellog as a cheap test organism for a variety of substances and herbal extracts; c) embryotoxicity assessment of herbal extracts using *Danio rerio* (F. Hamilton) (zebrafish); d) identifying multiple quality issues affecting weight loss Chinese food supplements, following signals indicating potential safety problems, including HPLC identification and quantification of sibutramine and phenolphthalein as adulterants (using a method developed and validated by us), microscopical analyses of the capsule powders, mass uniformity evaluation and a critical assessment of the formulation; e) developing computational models using multiple machine learning algorithms to predict drug hepatotoxicity using the DILIrank data set; f) analyzing the FAERS (FDA Adverse Event Reporting System) data made publicly available by FDA, with an assessment of the drug names and the risks of confusions, particularly in the case of using umbrella names; g) inventorying the drugs causing rash as an adverse drug reaction, using a detailed analysis of the summaries of product characteristics; h) microscopic identification and establishment of the histo-anatomical identification features of herbal products (an approach that is relevant for both safety and efficacy purposes).

With the second subsection of the first part (Non-clinical assessment of the efficacy of medicinal products and discovery of new medicinal products or other healthcare productst), I discussed several representative directions of research: a) a body of research carried out within a research project titled “Studies on the soil-plant-food-humans correlations in order to obtain a food supplement with a high content of herbal iron” (a patented extract for this purpose is discussed, together with other connecte research, such as the investigation of the content variation in polyphenols, flavones and iron in *Mentha x piperita* L. and *Petroselinum crispum* (Mill.) Fuss; our findings from multiple herbal products that ascorbic acid is virtually degraded in dried herbal products; our vast meta-research on iron contents in plants); b) a herbal extract developed by us to be used for the treatment of chemotherapy-associated neuropathic pain; c) QSAR models developed by us using machine learning algorithms for the prediction of substance effects on malignant melanoma cells; d) the use of global QSAR models and molecular docking to develop new inhibitors of c-Src tyrosine kinase; e) our meta-research (scoping review) on clinical trials using herbal products used for the dental caries prevention and their quality.

The third, short subsection of the first part deals with additional research directions for which did not have the time to show extensively: a) pharmacokinetics of B-ring unsubstituted flavones (an

extensive narrative review on this topic, the first one to be ever published); b) chemotaxonomy of lycophytes and ferns (discussing in a short paragraph our first volume on the topic, the first book of chemotaxonomy published at national level and one of the few published at international level); c) a (bioinformatics) analysis of the liver genes expressed under the influence of natural flavonoids; d) a re-analysis of the GSE18803 data set (generated by M. Costigan, A. Moss et al., 2009), performed with multiple bioinformatics tools; e) pharmacogenomics in the drug regulatory process: a European perspective.

As a summary, my research activity was disseminated through 37 papers in publication indexed by ISI Thomson, 13 papers indexed in other international databases, seven full-text works in other publications, over 60 works published as an abstract (with ISBN/ISSN), two scientific books (as a single author), 14 book chapters or books published as a co-author, 2 patents and 6 patent applications in the course of assessment.

The short second part discusses the evolution of my academic, scientific and professional career. I have graduated as a valedictorian (with a mean grade across the 5 years of study of 9.98 out of 10 and a mean grade in the graduation examination of 10.00 out of 10.00). My thirst for knowledge prompted me to also study law (at the Bucharest University; mean grade across the 4 years of study 9.87 out of 10; mean grade of the graduation examination 9.68) and later to get a master in Biostatistics (mean grade across the two years of study 9.91; graduation examination grade, 10.00 out of 10.00). I have followed many online computer science courses, being able to use the R computing and programming language, Python, SQL, XML, HTML and JavaScript. I have developed and updated the Cell and molecular biology course to correspond to the current knowledge in the field, as well as to the needs of our pharmacy students. I have introduced an optional Pharmaceutical law, very well received by our students. I have introduced a post-graduated course titled "Pharmaceutical regulatory affairs", the first of its kind in Romania, which attracts each year 20-40 students; this was followed by a regulatory affairs course on Marketing authorization variations, with similar student involvement. I have acquired a wide experience in the pharmaceutical field by working, besides the academic environment in the pharmaceutical industry (analytical method validation stability studies, quality assurance, regulatory affairs) and within regulatory authorities (Ministry of Health, National Medicines Agency). I have worked as an alternate EMA HMPC member and a full member of EMA CHMP and PDCO, and as a recognition of my efforts, in 2017 I was awarded the *Prix de la Pharmacie Francophone* by the French Academy of Pharmacy.

The last section of my thesis is focused on my further career development, consisting of Proposals for the development of the research and didactic activity. I plan to continue and develop my investigations of computation biology, bioinformatics and chemoinformatics, on the safety assessment of a variety of substances and extracts, on developing phyto- and nutrivicilance tools, pharmaceutical regulatory affairs, innovation and regulatory science, paediatric pharmacy and others. On the education side I propose the development of several curricular areas, to conclude with the old words of one famous biologist with broad horizons (Nehemiah Grew):

*"The Way is long and dark...If but little should be affected, yet to design more can do us no harm; for although a Man shall never be able to hit Stars by shooting at them; yet he shall come much nearer to them than another that throws at apples."*