

SUMMARY

The habilitation thesis titled “Applications of the Plant Biology in the Pharmaceutical Field for the Assessment of Toxicity and Therapeutic Potential of Chemical Compounds and Plant Extracts” is structured in three sections, according to the recommendation of CNATDCU and to the national legislation in force.

In the thesis the achievements obtained in the professional, academic and research activity after obtaining the PhD in Pharmacy title, in 1997, are inserted.

The first section, Scientific Activity, contains a presentation of the experimental research carried out in the above-mentioned period, within the Pharmaceutical Botany and Cell Biology Department of the Bucharest Faculty of Pharmacy, in collaboration with other departments (Pharmaceutical Chemistry, Organic Chemistry, Inorganic Chemistry, Pharmacognosy, Pharmacology, Biochemistry, Physical Chemistry) or other institutions (INB, USAMV Bucharest, The Faculty of Biology, Bucharest, Hofigal S.A. etc.).

The main research directions approached within my academic activity in the 1997-2016 period have been:

- ✓ Testing the toxicity of substances newly synthesized in the departments of Pharmaceutical Chemistry, Organic and Inorganic Chemistry and of herbal extracts (obtained from over 70 species, mostly angiosperms), by the *Triticum* bioassay – Constantinescu method;
- ✓ Morpho-anatomical and histochemical characterization of plant species and products, using (optical, digital and electronic) microscopic techniques;
- ✓ Phytochemical investigation of a diversity of plant species, both qualitatively (phytochemical screening, chromatographic techniques: TLC, HPTLC, HPLC, GC) and quantitatively (spectrophotometry, HPLC);
- ✓ The study of the biological and pharmacological effects of herbal extracts (research on the influence of plant extracts on normal and tumoral cells, establishing the animal acute toxicity, assessing the antidiabetic activity, assessing the topical antiallergic activity a.o.).

I. Testing the toxicity of substances newly synthesized and of herbal extracts by the *Triticum* bioassay (Constantinescu method) included a vast area of investigation:

I. a. Testing the toxicity of new substances synthesized within the *Pharmaceutical chemistry* department: O-acyl-oximino-dibenz[b,e]oxepine compounds; substances with a dibenzothiepine structure; N-(2-dialkyl-aminoethyl) substituted benzaldehydes; new derivatives of thiourea; compounds with a 4 (3H)-quinazolone structure; new acyl-oximines with 10,11-dihydro-5H-dibenzo[a,d] cycloheptene and 5H-dibenzo[a,d]cycloheptene general structures; new compounds, derivatives of O-acyl-oximino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene; new derivatives of N-(phenylcarbamothioyl)-benzamide.

I. b. Phytobiological testing of new substances synthesized within the Organic chemistry department: new diamides; compounds newly synthesized belonging to the classes of thiosemicarbazides, 1,2,4-triazoles, 1,3,4-thiadiazolilior and thiazolo[3,2-b][1,2,4]triazolones; new compounds with an 1,3,4-oxadiazole core, obtained by S-alkylation and N(3)-aminomethylation of -[4-(4X-phenylsulfonyl)phenyl]-1,3,4-oxadiazol-2-thioles, X=H, Cl, Br; new compounds of the N-acyl-amino acid, 1,3-oxazol-5(4H)-one, α -acylamino ketone and 1,3-oxazole classes; compounds from the class of 5H-dibenzo[a,d]cycloheptenes; new compounds with benzimidazole 2 and 1,2-substituted structure.

I. c. Phytobiological testing of new substances synthesized within the Inorganic chemistry department: Zn(II)-porfirines complex combinations; Cu(II)-porfirines complex combinations.

I. d. Toxicity testing of plant extracts (extractive solutions):

- Total aqueous, ethanolic, hydro-ethanolic extracts or fraction thereof were obtained from over 70 species of angiosperms, less of gymnosperms or ferns and fern allies, some cultivated for ornamental or food purposes, others from the spontaneous flora, used in the traditional medicine or known as invasive plants (*Cydonia oblonga* Mill., quince (*Rosaceae*), *Abutilon theophrasti* Medik., velvetleaf (*Malvaceae*), *Ranunculus ficaria* L., lesser celandine (*Ranunculaceae*), *Trigonella caerulea* L. Ser., Blue fenugreek (*Fabaceae*), *Arachis hypogea* L. peanuts, (*Fabaceae*), *Cuscuta campestris* Yunck., dodder (*Cuscutaceae*), *Dieffenbachia seguine* (Jacq.) Scott., dumbcane (*Araceae*), *Anthurium andraeanum* Linden ex André., flamingo flower (*Araceae*), *Mespilus germanica* L., common medlar (*Rosaceae*), \S .a.
- Comparative studies of extracts obtained from herbal products also made the object of two research contracts, ongoing or recently closed. In this sense, the hydroalcoholic extracts obtained from the leaves of *Cynara scolymus* L., *Amaranthus hypochondriacus* L., *Plantago lanceolata* L., *Rubus idaeus* L., *Morus alba* L. ("Development of a herbal medicinal product for topical use in allergic dermatoses", financing contract PN-II-PT-PCCA-2013-4-1953, no.199/2014, project director prof. Mihaela Dinu, PhD) and the hydroalcoholic extracts obtained from four herbal products: *Amaranthus retroflexus* L., *Lavandula angustifolia* L., *Raphanus sativus* L., *Cirsium arvense* L. ("Investigation of the antidiabetic potential of several herbal extracts", bilateral contract, University of Medicine and Pharmacy „Carol Davila” Bucharest, Romania – State University of Medicine and Pharmacy “Nicolae Testemițanu”, Chișinău, Republic of Moldova, Competition “N. Testemițanu”, contract no. 11/2013, project director prof. Mihaela Dinu, PhD) were analyzed.

II. In a large number of investigations I have applied **microscopical techniques** for the identification and morpho-anatomical characterization of a number of herbal species and products. The microscopical methods were used in the botanical study for the identification of structures characteristic for the vegetative and reproductive organs of potentially phytoactive species or for the establishing of a set of anatomical and histological elements necessary for the identification of herbal products phytotherapeutically active. Mostly spermatophyte species

(angiosperms and to a lesser extent, gymnosperms), but also ferns (e.g. *sp.*, *Nephrolepis sp.*), fungi (*Agaricus sp.*, *Boletus sp.*) or lichens (*Usnea sp.*) were analyzed microscopically. I have used several types of microscopic preparations: cross-sections, surface preparations, herbal powders, and histochemical preparations, which have been analyzed by:

- a) a light microscope;
- b) a digital microscope;
- c) a scanning electronic microscope.

III. A phytochemical investigation was carried out for numerous herbal species (angiosperms, less ferns or fungi – over 70 herbal species) by phytochemical screening, chromatographical techniques: TLC, HPTLC, HPLC, GC, spectrophotometry).

IV. The study of the biological and pharmacological effects of a number of herbal extracts was carried out mostly in collaboration with researchers from the Pharmacology department of the Faculty. Investigations on the influence of herbal extracts on normal (Vero– derived from green African monkey kidneys) and tumoral (RD– rhabdomyosarcoma) cells were also performed in collaboration with researchers from the National Institute of Research and Development for Microbiology and Immunology I. Cantacuzino (INCDMI Cantacuzino).

More recent studies have approached themes included in two research contracts: establishing the acute toxicity in mouse, assessing the antidiabetic activity of hydro-alcoholic extracts obtained from four herbal products (*Lavandula officinalis* L., *Cirsium arvense* L., *Raphanus sativus* L., *Amaranthus retroflexus* L.) in rat with diabetes induced by alloxan (bilateral contract no.11/2013, with the Faculty of Pharmacy from Chişinău, Republic of Moldova), developing an experimental model of atopic dermatitis, assessing the topical antiallergic activity of six dry herbal extracts – the efficacy of dried extracts in an experimental model of contact hypersensitivity induced in BALB/c/Br mice (contract no. 199/2014, PNII).

The second section of the habilitation thesis includes a **short presentation of my didactic evolution**, starting since 1991, when I became by competition a university assistant professor at the Pharmaceutical Botany and Cell Biology Department. Thereafter I occupied, by competition as well, the positions of lecturer (1997), associate professor (2003) and university professor (2014). The didactic activities consisted in conducting laboratory works and courses for the students of the Faculty of Pharmacy from years I and II and, for a short period, for those from FMAM (the Faculty for Midwives and Nurses), for pharmacy technicians, coordinating 57 student dissertations and 32 scientific works presented at Student Scientific Sessions, conceiving questions for entrance examination or entrance examination simulations.

The academic activity was materialized in publishing 13 books (3 as a single author, 10 as a co-author, and of these, 4 as a main author). The results of the research activity were disseminated by publication of 79 full text papers, of which 30 in journals indexed ISI Web of Knowledge and 39 indexed in other international databases.

The experience in the research in the field of herbal medicinal development may also be highlighted by my participation in an educational project and in 9 research teams within various national programmes, won by competition, two as a project director (2013-2015, 2014-2017) –

one bilateral and the other, collaborative project of applicative research (PNII), two as a partner team leader for UMFCD (2004-2006), 5 national projects as a member of the research team.

The third section includes the development plan for the academic, professional and scientific research career. The objectives of the research activities consist in increasing the competitiveness of research, developing new partnerships in the fields of interest and solving complex problems associated with previous research areas. On a long term, I will approach research on: **finding plant species involved in controlling environmental pollution (soil, atmosphere air, precinct air, water)**, creating “green filters” in places with problems caused by accumulation of toxic substances: heavy metals, volatile organic compounds etc; **establishing the differential morpho-anatomical characters between chemotaxons and species very similar morphologically**, using the light and electronic microscopy, useful in the activity of collecting medicinal plants; **using medicinal plants, of herbal medicines and of food supplements in various socio-cultural environments, based on responses to surveys developed specifically for this purpose (and statistically processing those questionnaires); extending the therapeutic potential of herbal species, identifying new therapeutic activities by using other plant organs as raw materials than those used traditionally or by finding new pharmacologically active compounds (interdisciplinary collaboration); ethnobotanical practices in various areas of the country; identifying research problems of the manufacturers of medicinal products related to research directions by initiating themes of interest for them).** For the development of the scientific career I propose the following: continuing the research activities within the ongoing projects; publishing papers in journals of high international visibility; new proposals of research projects in various national and international programs; the completion of my annual list of publications with at least two papers published in journals indexed ISI Web of knowledge with high impact factor and relative score of influence; maintaining the dialogues initiated with various potential economic beneficiaries. I also intend that my future scientific activity be oriented mainly on the same research directions in which I have obtained significant results, taking also into account the development of related directions.

Within the didactic activity I will contribute in a close connection with the members of the Department of Pharmaceutical Botany and Cell biology to the conception and writing of didactic materials necessary for the students and others.

Thus, in both the didactic and research activities, I intend to update my professional knowledge by participating to national and international conferences, but also by organizing such scientific events by which international specialists and scientific personalities may come in our country. Thus close professional relationships with partners from research and university centers will be established and maintained.

My whole activity will be oriented to shape and develop competent professionals in the field of the pharmaceutical research and practice.

In my academic, professional and scientific research career, I will continue my personal and professional development, so that the educative and research activities in which I will

involve, may correspond to high quality and ethical requirements specific for the European university environment.

Prof. Mihaela Dinu, PhD