

CONTRIBUTIONS TO THE SCIENTIFICALLY VALIDATED VALORIZATION OF PLANTS EMPLOYED IN TRADITIONAL PHYTOTHERAPY

THESIS ABSTRACT

This habilitation thesis presents, in a synthetic manner, the main results of the author's scientific, professional and academic achievements in the time frame 2006–present, following the obtainment of the PhD degree. The research activities were performed in the field of Pharmaceutical Botany, and focused on the investigation of plants and plant-derived natural products with the aim to promote the advanced valorization of the ethnomedical heritage according to modern pharmaceutical requirements. Important goals were to obtain new data underpinning the utilization of plants employed in traditional phytotherapy, and the preparation of products with optimized biopharmaceutical properties. Research was performed from three major perspectives: phytochemistry, bioactivity and botanical microscopy.

The main subject of the author's research is *Cotinus coggygria* Scop., a shrub belonging to the Anacardiaceae family. The traditional utilization of the plant was noted during botanical field trips in the area of the Aninei Mountains. Lipophilic extracts of the wood were cited by locals to have excellent cicatrizing effects and incited subsequent research on the diethyl ether-soluble fraction of the heartwood. Fourteen polyphenolic compounds were isolated and their chemical structure was assigned based on one- and two-dimensional NMR. Their content in the heartwood and branches of various diameters was established, using a new HPLC-DAD method elaborated by the author. Of the assessed compounds, one (the C-3/C-3" dimer of 3',4',7-trihydroxyflavanone) was reported for the first time from the plant Kingdom and represents a newly identified phytocompound. Three other compounds were isolated for the first time from members of the Anacardiaceae family: 2,3-dihydroquercetagenin is a very rare flavanone derivative signaled before from *Wendita calysina* (Geraniaceae). The procyanidins fisetinidol-(4 α →8)-(+)-catechin and epifisetinidol-(4 β →8)-(+)-catechin are mostly known from wattle extracts (Fabaceae) and pine bark (Pinaceae). Their identification in smoketree wood is important from a chemotaxonomical point of view, but as well a biomedical, as they are strongly antioxidative. Furthermore, a mixture of isobaric

flavonoid dimers with new unreported structures was obtained. Final aspects of the isomers structural assignment are ongoing. All these compounds are valuable markers for *C. coggygria* extracts in investigations bearing on the authentication of herbal preparations intended for medicinal purposes.

In Europe, the use of *C. coggygria* is restrained to local ethnomedical practices concerning the treatment of injuries and mucosal irritations. These indications are however quite stable across the continent, and their scientific validation has been the subject of research in the last decades. The author investigated anticancer, anti-inflammatory, and acetylcholinesterase inhibitory effects, expanding the spectrum of known properties for smoketree extracts. The subjects of the research were extracts and representative pure compounds (sulfuretin, butein) obtained from the heartwood of smoketree. These natural products have poor water solubility; the improvement of their bioavailability was as well targeted. To this end, cyclodextrin derivatives were prepared, characterized and tested on cultures of various cell lines, and in the mouse ear edema. Comparisons between the bioactivity of free and complexed natural products were performed. In case of the acetylcholinesterase inhibitory effects, bioactivity guided fractionations were performed and sulfuretin, butein, fisetin and quercetin were the most active compounds in the enzyme assay. Effects were further evaluated after intra-cerebroventricular administration. Besides research on extracts and metabolites from *C. coggygria*, the author contributed to the investigation of other plant products as well, including Japanese knotweed (*Reynoutria japonica* Houtt.), licorice (*Glycyrrhiza glabra* L.), birch (*Betula pendula* Roth), and various bud extracts.

Another research line is the light microscopic investigation of medicinal plants, representing an important focus of bachelor's and master's thesis coordinated by the author in the last decade. Botanical microscopy uses specific histological and anatomic features of herbal materials to confirm or to exclude the identity of medicinal plant products. It is a basic method for the identification of adulterations and authentication of herbal medicines, and is included in all pharmacopoeias. Its main advantages are the non-destructive character, its lack of costs (except the availability of a microscope), and low analysis time. The anatomic studies performed or coordinated by the author afford a rich set of representative photographs which document structural features of medicinal plants. Particular aspects of the author's research in this field are the assessment of innovative microscopy dyes, the use of Folin-Ciocalteu reagent as a

microchemical tool in the localization of polyphenols, and the association of fluorescence microscopy for the complementary localization of autofluorescent metabolites in cross-sections.

Collectively, after the obtainment of the PhD degree, the author published more than 50 fulltext scientific papers – 26 listed on ISI Web of Science (14 as main author) and numerous congress papers. According to the Web of Science, the Hirsch index is 7; the sum of times cited without self citations is 123, the number of citing articles without self citations is 113; average citations per article 3.8. The habilitation candidate authored five articles published in journals ranked by UEFISCDI (Romania) in the categories “red area” (3 articles) and “yellow area” (2 articles), and by the Web of Science in the first (Q1) and second (Q2) quartiles of their field. As well, she authored nine books and three international book chapters. Research was performed by the candidate in the framework of eight grants receiving national or international financing. The activities performed in Innsbruck (Austria) during the three projects granted to the Institute of Pharmacy and Pharmacognosy had a decisive role in the professional development and accomplishments of the author.

In recognition of scientific achievements during by the Romanian-French bilateral project PN II-CT-789/30.06.2014, the habilitation candidate was awarded a Diploma of Excellence (21.11.2016). Teaching performances were awarded with the title “Bologna Professor” by the National Alliance of Student Organizations of Romania (19.05.2017). The author is a reviewer for several scientific Journals: Pharmacological Research, Environmental Pollution, International Journal of Molecular Sciences, Molecules, Evidence-based Complementary and Alternative Medicine, Recent Patents on Drug Delivery and Formulation, and Notulae Botanicae Horti Agrobotanici Cluj-Napoca.

Regarding the teaching activity, the author was in Romania one of the first to publish a lecture book on plant systematics using the new molecularbiologic classification elaborated by the Angiosperm Phylogeny Group (Antal DS. *Biologie vegetală pentru studenții Facultății de Farmacie*, Ed. Mirton, Timisoara, 2007, ISBN 978-973-52-0148-7). The lectures and lab classes of Pharmaceutical Botany are constantly upgraded by adding novel scientific information and subjects/chapters, according to international developments in this field. Additional chapters focusing on and the chemical ecology of plant metabolites, on the elicitation of allergies by plants, as well as on updates concerning the pharmaceutical importance of Fungi and Algae are planned.

The accent on the development of independent, critical thinking as opposed to memorization, and the interconnection of academic knowledge to everyday life are constant objectives throughout the teaching activities of the author. The development of academic on-line resources in the field of medicinal plants is as well intended.

The goals for future scientific activity include the investigation of medicinal plants with emphasis on issues of quality control, drug discovery and taxonomical relationships. The author intends to develop Romanian ethnopharmaceutical studies, to consolidate the scientific validation of plants having a background in traditional medicine, to obtain advanced formulations based on natural products (including nanoparticles), and to develop *in planta* localization techniques for secondary metabolites in plants. These aims are to be achieved in collaboration with workgroups from Romania and abroad. The submission of research proposals and the obtainment of funding will be a continuous goal in order to secure financial resources for the development of the existing research facilities and as well for the development of human resources involved in research.