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INTERDISCIPLINARY RESEARCH FOR ASSESSEMENT OF HEALTH SERVICES AND PRODUCTS

ABSTRACT

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The habilitation thesis "Interdisciplinary research for the evaluation of health services and products" is structured in two sections. In the first section, the most important results of the research activity carried out by the author, after obtaining the title of doctor of science, in the field of Pharmacy, are presented. In the second section, the main stages of the evolution of the professional and didactic career, as well as the targeted research directions, are pointed out.

Increasing the quality of life of patients is a priority objective of stakeholders in the health field and it can be achieved by providing safe, effective, with the highest quality, accessible and with the lowest costs health services and products. For this reason, marketing, post-marketing and legislative research complement the efficiency and safety studies undertaken, having a significant role in expanding knowledge in the health field.

The marketing research presented in the first chapter was carried out after completing the doctorate and complements the studies presented in the doctoral thesis. Thus, in these studies, pharmaceutical services provided by pharmaceutical care and clinical pharmacy activities were described, as well as the marketing strategies adopted by pharmaceutical units during periods of crisis, such as the COVID-19 pandemic and the economic-financial crisis of 2008. The COVID-19 pandemic has led pharmaceutical assistance to a new stage, pharmacists having to resort to new solutions for the provision of pharmaceutical care services: distributing services and products in new locations (e.g.: Fangcang-type hospitals), disseminating scientific information through different media channels, establishing tele-pharmacy services and the use of mobile phone applications for therapy monitoring (e.g.: anticoagulants). Many of these solutions can be taken over in current post-pandemic pharmaceutical practice. On the other hand, the role of clinical pharmacists was also amplified, so that the services provided by them included many new aspects related to COVID-19 both by providing services and information for patients or the population, and by collaborating with doctors to manage the pandemic or by identifying medical solutions appropriate to the new epidemiological context. Later, the responsibilities of managers or owners of pharmaceutical units during the pandemic were presented.

Complementary to the accessible and quality services and products provided to patients, economic efficiency has a major role for the smooth running of the activity of the pharmaceutical units and their viability. Therefore, economic crises such as the one in 2008, can affect the economic-financial stability of these units. In a study, some measures to reduce expenses were proposed, such as: stopping additional hiring, reducing expenses related to staff salaries, outsourcing services, etc. At the same time, various strategies were described to make the activity of pharmaceutical units more efficient, some of them being: the creation of strategic partnerships of distributors

by managing a common car fleet, partnerships of pharmacies for the purchase of products, vertical integration "upstream" or "downstream", the horizontal integration of the activity, the establishment of a minimum profitability threshold per cost centers, the financing of the activity through "factoring" (taking over debts by financial companies), etc.

As a complement to the solutions described above, during the pandemic, strategies were identified to diversify the portfolio of products and services adopted by pharmaceutical units around the world: the establishment of drive-thru pharmacies, the online sale and home delivery of medicines, the introduction of services for testing and vaccination for COVID-19 in pharmacies, preparation of antiseptic agents, patient triage, information and counseling regarding the pathology of COVID-19, the involvement of pharmacists in combating the toxic "infodemic", etc. Therefore, it can be stated that in times of crisis, it is not enough only to adapt the activity of the pharmaceutical units to the new context, but it is necessary to adopt some government measures to support them.

Another marketing research aimed at evaluating the perception and satisfaction of patients towards the health system in our country, through an exploratory and descriptive transversal study. Measuring patient satisfaction with the quality of medical services is a significant element of the health system evaluation. It is the starting point for the creation of national health policies. With the help of exploratory and descriptive research, the factors that influence the perception and satisfaction of patients were identified. Data were collected through face-to-face interviews with patients based on a questionnaire. Of all the respondents, 58% declared that they do not trust the health system. Accommodation, food and other facilities of Romanian hospitals were perceived to be at a low level, and a third of the respondents were dissatisfied and very dissatisfied with their overall impression of the healthcare system in Romania. In this study, a statistically significant relationship was established between trust in the healthcare system and patients' age, respectively gender, as well as between the general impression of the healthcare system and the age, respectively the income of the patients.

The second chapter of the thesis was dedicated to the post-marketing studies carried out regarding health products. This part included studies on pharmacovigilance, cosmetovigilance, nutrivigilance, studies on antibiotic resistance, pharmacoeconomic research, but also studies on patients' assessment of the benefits and risks of contraceptive drugs. The pharmacovigilance studies presented in the thesis concerned various drug classes: statins, antidiabetics, gonadotropins, vaccines against COVID-19. Thus, using secondary sources such as the EudraVigilance and VigiBase databases, descriptive analyzes were carried out regarding the frequency of

reporting of some adverse reactions, such as psychological reactions to statins (completed with disproportionality analysis compared to antiplatelet and antihypertensive drugs), thrombosis associated with death in vaccines against COVID-19, serious adverse reactions reported to gliflozin caused by potential interactions, etc.

According to the MedDRA classification, antibiotic resistance falls under the category of spontaneous adverse reactions that must be reported to the authorities, although it is often overlooked. For database reporting, there are several preferred terms that can be used (e.g.: “drug resistance”, “multiple-drug resistance” and “pathogen resistance”). Therefore, a first study started in this direction consisted of the presentation of the most important aspects related to the mechanisms of the emergence of bacterial resistance to antibiotics, the therapeutic options for infections caused by these bacteria, as well as the current directions of research and development of therapies to combat this scourge. Given that shortly after the introduction of antibiotics into therapy, clinicians discovered antimicrobial resistance, contemporary society is faced with this serious public health problem, leading to increased morbidity and mortality worldwide. The main mechanisms by which bacteria develop antibiotic resistance include changes in the drug target, prevention of cell entry, elimination by efflux pumps, or drug inactivation. A better understanding and prediction of a pathogen's resistance patterns will lead to a better selection of active antibiotics for the treatment of multidrug-resistant infections. Therefore, the study undertaken shows that the minimization of the rate of emergence of resistance can be achieved through a detailed knowledge of resistance mechanisms and effective therapeutic options, the initiation of political-legislative measures, the avoidance of self-medication, improper prescription and use, as well as the need for authorization of new molecules or alternative therapies.

In a study focused on the assessment of the risks of the administration of food supplements, we showed the need to develop the activity of nutrivigilance in order to detect, evaluate, understand and prevent adverse events. In this study, it was shown that in the EU, including Romania, there are some regulations regarding supplements, but which do not refer to the detection, monitoring or collection of adverse reactions of food supplements. Taking into account the intrinsic risk of food supplements, as well as their possible interactions with various drugs, it was emphasized that the Romanian authorities should start the nutrivigilance activity, following the example of other countries, and the involvement of pharmacists in this activity could contribute considerably to reducing these risks.

Cosmetovigilance was another point of interest of the author. Thus, in a study on the advantages of using hyaluronic acid and its combinations with various bioactive compounds, aspects regarding the safety of these plant extracts were described. Based on the studied literature, plant extracts incorporated as ingredients in marketed

products are considered mostly safe, but nevertheless some minor adverse events (irritation, sensitization, contact allergy) have been reported. A number of 47 species of plants have been identified in the composition of cosmetic products with hyaluronic acid. For the topical preparations that contain 20 of the 47 ingredients, no publications have been identified regarding their toxicity, and for the other 27 there are data in the literature that show a potential risk of adverse events when administered cutaneously. The other incorporated compounds (probiotics, amino acids, peptides, proteins, vitamins, saccharides or other active compounds such as allantoin, lactic acid, lecithin, urea, superoxide dismutase, gold, malachite extract) are considered safe ingredients in cosmetic products, presenting a good skin compatibility. However, minor side effects such as contact dermatitis have been reported.

Patient accessibility to treatment is a principle of health insurance. The allocation by the authorities of the funds necessary for the prevention and treatment of diseases is an essential component of therapeutic success, of increasing adherence to treatment and implicitly of increasing the quality of life of patients. Pharmacoeconomics studies represent another direction of post-marketing research addressed by the author. The pharmacoeconomic research initiated as part of the doctoral thesis was continued in a study in which an exploratory research extended over 18 years was carried out, regarding the economic impact of diabetes in the Single National Health Insurance Fund. Based on the National Diabetes Program, antidiabetic drugs and other products (glucose self-monitoring tests, testing of glycosylated hemoglobin, insulin pumps and consumables for these pumps) are provided free of charge. Throughout the analyzed period, the diabetes program has undergone many changes related to the method of procurement of medicines and devices by patients. The retrospective longitudinal study undertaken shows that the average share of funds allocated for the treatment of diabetes patients in the total funds allocated for health programs was 21.3 ± 3.4%, and the average growth rate of these funds was 25.4 % ($r = 0.488$, $p = 0.047$). On the other hand, during the 18 years, the funds increased more than 14 times, despite the fact that the number of patients increased only about 2.5 times. The average number of patients treated per year was 667,384 ± 94,938 ($r = 0.73$, $p = 0.016$), and the cost of treatment was 215 ± 36 EUR/patient/year. The present study also shows a statistically significant correlation ($r = 0.815$, *** $p < 0.001$) between the cost/patient/year (EUR) and the funds allocated for diabetes in Romania/year (EUR). The average value of the cost of antidiabetic drugs was 96,045 ± 67,889 thousand EUR, and of other expenses (glycosylated hemoglobin determination, self-monitoring tests, pumps and consumables for insulin pumps) was 11,530 ± 7922 thousand EUR ($r = 0.945$, $p < 0.001$). The long-term control of the disease results in reducing the risks of complications and implicitly the costs. The results obtained from the evaluation of the physical and efficiency indicators could represent an important

support for the institutions involved, to generate policies or strategies for the health system or to help use public funds more efficiently. Even if the cost is increasing, the correct and optimal treatment is a main condition for the health of the diabetic patient and for the prevention of its complications, which have multiple socio-economic repercussions.

Also in the framework of post-marketing research, the patients' perception of the benefits and risks of using contraceptive drugs was evaluated. Studies show that the number of women who have used contraceptive drugs is constantly increasing. Some of the positive aspects captured in these studies are represented by the provision of specialized information by doctors and pharmacists, the patients' knowledge of their main benefits and risks. A surprising negative aspect shows that, in Romania, women start using contraceptives, often following the advice of unauthorized persons and without performing any prior medical check-up. Given their risks, contraceptives should not be used as self-medication, but this requires women to be properly informed, regardless of their socio-economic status, religion, area of residence, level of education, occupation, marital status or any other factor. The improvement of the situation could be achieved through the existence of a health system that covers the expenses for specific tests, as well as with the help of health professionals who should emphasize the importance of a complete medical examination before the administration of contraceptive drugs.

The third chapter of this work is dedicated to the analysis of the legislative regulations in the medical field. The legislative regulations regarding the establishment of pharmacies and pharmaceutical warehouses were analyzed in various retrospective studies using the comparative method, the logical analysis and the interpretation method. Among the topics studied can be listed the analysis of legislation related to: (i) the establishment of pharmaceutical units after 1990, (ii) the authorization and operation of wholesale distributors, (iii) the analysis of national and European regulations regarding the notification of food supplements, as well as (iv) marketing of protective masks in pharmacy (so requested during the COVID-19 pandemic), allowed under the Pharmacy Law no. 266/20008. The last study regarding protective masks is completed with the presentation of some aspects regarding the CE marking and the declaration of conformity, mandatory elements for the introduction of medical devices on the European market. Also within this chapter, recommendations of the authorities or professional bodies as well as various legislative regulations that influenced the activity of the pharmaceutical sector during the pandemic are captured: (i) emergency authorization, (ii) the possibility of renewing prescriptions for chronic diseases by pharmacists (France, Ireland, Italy, Malta, Portugal or Serbia), and even prescriptions with hypnotics, anxiolytics, narcotics and opiate substitution treatments (Austria, Brazil,

Canada, France, etc.); (iii) replacing classic paper forms with electronically transmitted prescriptions; (iv) the work schedule of pharmacies; (v) preventing drug shortages or price increases; (vi) "Mask 19" code for identifying and protecting victims of domestic violence during the pandemic.

The quality of health products is a major concern of stakeholders in the health system. Thus, in the fourth chapter, research is presented on the characterization and evaluation of active ingredients and health products. Taking into account the antioxidant properties of grape pomace and forest fruits (bilberries, red currants), the development of a food supplement based on these ingredients was proposed. The pharmaco-technical research carried out shows that the powder can be encapsulated without difficulty (compressibility index 14.71% and Hausner ratio 1.17), and the phytochemical and antioxidant capacity testing show that the obtained product meets the quality requirements and offers a wide range of phenolic compounds that could have benefits in preserving of human health and the preventing of several chronic diseases.

Other studies in the field of food supplements aimed at the validation of modern, cheap and fast methods for the assay of some compounds from these products (ubidecarenone, zinc). Thus, an HPLC method was developed for the assay of ubidecarenone from five products conditioned in the form of soft gel capsules or hard gel capsules. On the other hand, a spectrophotometric method comparable to other methods was proposed for the zinc assay. The two methods developed for the assay of ubidecarenone and zinc in food supplements are precise, simple, cost-effective and fast and can be used by manufacturers to certify the quality of manufactured products.

Other studies focused on the characterization of some plant extracts by chromatographic techniques. Two extracts of *Orthosiphon stamineus* Benth. were analyzed by reverse-phase thin-layer chromatography and reverse-phase automated multiple development, respectively. The characterization of the studied extracts was achieved by separating and identifying two main classes of compounds: caffeic acid derivatives (rosmarinic acid) and polymethoxylated flavonoids (sinesetin and eupatorin). In another study, a comparison was made of the terpene profile of different rosemary extracts (volatile oil, dried plant tincture, fresh plant tincture, glycerin macerate). Although, the study showed that the same terpenes were identified in the four samples, the percentage composition of the major compounds was different in these samples. The major components of the essential oil and glycerin macerate were 1,8-cineole, α-pinene, and camphene, and the tinctures were found to be rich in α-pinene. Thus, the evaluation of the qualitative and quantitative differences of the most important terpenes can allow the selection of those extracts appropriate from the point of view of the chemical composition correlated with a certain therapeutic action.

Other research focused on the incorporation of plant extracts into various pharmaceutical forms and the evaluation of the resulting products. Thus, the hydroalcoholic extract of *Aristolochia clematitis* L. was incorporated into a viscoelastic hydrogel based on methylcellulose and evaluated from the point of view of its stability. Later, the organoleptic characteristics (appearance, viscosity, smell and color) were determined, as well as the pH and dispersion capacity of the formulated hydrogel. Both at the time of preparation and 6 months after preparation, the evaluated parameters are within the limits of acceptance.

On the other hand, with the help of an animal model of skin carcinoma (quick and easy to reproduce), accelerated by type B ultraviolet radiation, the effects of topical application of lupeol incorporated in a complex with hydroxy-propyl-gamma cyclodextrin (HPGCD) were evaluated), in a 1:1 ratio. Lupeol induced an improvement in all skin physiological parameters (TEWL, sebum, melanin, erythema, skin hydration). According to these results, lupeol developed an important chemopreventive activity in the skin. In another study, the pro-apoptotic capacity of soy extract alone and after incorporation into lyotropic liquid crystals was evaluated. This ability was tested using B164A5 mouse melanoma cells, and the results show that soy extract exhibits apoptotic properties against this cell line, and incorporation into lyotropic liquid crystals does not adversely affect this property.

The evaluation of the antimicrobial efficiency of the combination of fatty oil from corn germ and 100% certified organic sea buckthorn oil was the subject of another research. This combination can be used both as a vehicle and as an active ingredient in pharmaceutical products for oral use, due to the intrinsic antimicrobial properties of the mixture. The study was carried out in accordance with the monograph "Antimicrobial conservation effectiveness" from the European Pharmacopoeia 7th ed., demonstrating the antimicrobial effect on the following standard microorganisms: *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 9027, *Candida albicans* ATCC 10231 and *Aspergillus brasiliensis* ATCC 16404.

Cosmetic formulations are also included in the category of health products. A first topic concerned the evaluation of ingredients with emollient properties by making two formulations for hand creams with two different ingredients: (1) synthetic oil (hydrogenated polydecene) and (2) a mixture of Jojoba esters. The quality control consisted in performing the following appearance, color, smell and physical determinations (pH, viscosity), and the effectiveness assessment consisted in identifying the sensation perceived on the skin after applying the cosmetic product by 10 female persons. The results of the study show that there are no differences between vegetable oils and synthetic oils, both preparations showing adequate properties. The same parameters were used to evaluate a regenerating hand cream formulated with the natural ingredients C10-18 triglycerides from palm oil compared to another

formulation based on synthetic oil. Both formulations presented a good degree of acceptability both at the time of preparation and 30 days after. Moreover, the product based on natural oil was perceived by all subjects as having a strong moisturizing effect. Another category of ingredients used in cosmetics that can affect their quality is represented by preservatives. Therefore, two moisturizing creams were formulated, one based on a traditional preservative (paraben mixture) and another with an alternative preservative containing glycol, glycerin, glyceryl caprylate, phenylpropanol (recommended concentration 0.5-1,5%). The physico-chemical characteristics (pH and viscosity), organoleptic control (appearance, color and smell) and antimicrobial efficacy test show that it is possible to develop cosmetic care products with the help of alternative preservatives. To evaluate the quality of a serum intended for the care of the periorbital area, accelerated stability studies were performed. Organoleptic control (appearance, color and smell) and pH determination at the time of preparation and 30 days later show that the formulated cosmetic product is stable and there was no damage to the packaging in which it was conditioned. The qualitative and quantitative determination of tocopherol acetate in an anti-aging day cream complements the studies carried out in the field of cosmetics. The sample was analyzed by a gas-chromatographic method, and the results obtained show a good recovery of α-tocopherol from the studied product. The method shows good selectivity, adequate limits of detection and quantification and can be applied in the routine analysis for the quality control of cosmetic preparations containing α-tocopherol.

Experimental animal studies were used to evaluate some biological effects of alpha-lipoic acid, as well as *Olea europea* L. extract. A first study aimed to evaluate the effects after discontinuous administration of alpha-lipoic acid in animals with cardiometabolic disorders induced by an increased intake of fructose. The treatment reduced fructose-induced disturbances (alteration of carbohydrate and lipid metabolism, increased systolic blood pressure, hepatocytolysis and a general pro-inflammatory and pro-oxidant status), confirming its antioxidant and pleiotropic properties. Subsequently, the cardiovascular and metabolic effects were evaluated in heart failure with preserved ejection fraction associated with obesity. Under experimental conditions, discontinuous treatment with alpha-lipoic acid prevented weight gain and attenuated disturbances of glucose and lipid metabolism. Furthermore, it prevented the development of cardiac hypertrophy and attenuated the onset of diastolic dysfunction. The results obtained in the presented studies show the promising potential of alpha-lipoic acid treatment in cardio-metabolic disorders. Other experimental studies have been carried out to evaluate the effects of olive leaf extract (*Olea europea* L.). The results show diuretic, possibly antihypertensive, antioxidant, hypoglycemic effects, improvement of the lipid profile, etc. All these demonstrate that metabolic disorders and associated oxidative stress were ameliorated by *Olea*

europaea L. leaf extract, which could open new perspectives in the adjuvant treatment of cardio-metabolic syndrome.

The last research topic presented in the thesis is aimed at describing modern systems for transporting active substances to the target, knowing that the conventional treatment of many diseases (oncological, immunological, infectious, etc.) has many disadvantages that limit their use. In this context, dendrimers and therapies based on biopolymer - pro-drug systems represent promising alternatives for improving the pharmacokinetic and pharmacodynamic properties of drugs and reducing their toxicity. Dendrimers (synthetic polymers characterized by branched repeating units starting from a focal point and possessing a large number of terminal functional groups) have proven to be valuable formulations for both diagnostics and therapy due to their ability to improve solubility, absorption, bioavailability and target release. Antineoplastic dendrimer research has been widely developed, and several types of complexes of poly(amidoamine) and poly(propylene imine) dendrimers with doxorubicin, paclitaxel, imatinib, sunitinib, cisplatin, melphalan, and methotrexate have shown improvement compared with the drug molecule used alone. Likewise, various dendrimeric complexes with anti-inflammatory drugs (e.g. ibuprofen, indomethacin, piroxicam, ketoprofen and diflunisal), antibiotics (e.g.: fluoroquinolones, macrolides, beta-lactams and aminoglycosides, etc.), antivirals (e.g.: tenofovir, maraviroc, zidovudine, oseltamivir and aciclovir, etc.), radioisotopes, etc. were developed and studied. Gene-directed enzyme-activated prodrug therapy (GDEPT) has been intensively studied as a promising new prodrug delivery strategy, with its main advantages being increased efficacy and reduced toxicity. In recent years, numerous therapeutic systems based on the GDEPT strategy have entered clinical trials. Research focuses on the development of non-viral vectors due to their low immunogenicity, high specificity, ease of synthesis, etc. On the other hand, therapies based on biopolymer-prodrug systems also represent a promising alternative for improving the pharmacological properties of drugs, as well as for reducing their toxicity. Polymer-directed enzyme-activated prodrug therapy is based on tumor cell targeting and drug release using polymer-drug and polymer-enzyme conjugates. Numerous antitumor molecules have been conjugated with natural polymers (chitosan, hyaluronic acid, dextran, pullulan, silk fibroin, heparin), some complexes being in advanced stages of clinical study.

In the second section of the thesis, the professional experience carried out in the pharmaceutical units is presented, as well as the didactic activity and the involvement in the academic management within the "Lucian Blaga" University of Sibiu and the "Vasile Goldiş" Western University of Arad of the author.

The university career development plan structured in the two components, didactic and scientific is presented at the end of the habilitation thesis. Thus, on the didactic level, the author proposes to continue approaching the subjects taught in an ethical and professional manner, as well as introducing new courses into the curriculum. Also, the future research directions are represented by the continuation of some of the current research themes, but also by the approach of new topics (e.g.: anti-doping legislation, evaluation of resistance to antifungals, anticholinergic drug loading, monitoring of some adverse reactions identified when administering some frequently used drugs, pharmacoeconomic studies, market positioning studies of various health services or products, etc.), which underline his ability to guide doctoral student.