REVIEWS

OF THE DISSERTATION WORK FOR AWARDING THE DOCTOR OF SCIENCE ON THE IDENTIFICATION, ANALYSIS AND ASSESSMENT OF PHARMACOKINETIC AND PHARMACODYNAMIC MEDICINAL PRODUCTS

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The dissertation is devoted to one of the most current problems in modern drug therapy: taking into account the risk of undesirable drug interactions in the use during treatment not only of a combination of different prescription medicinal products, but also a combination of medicinal over-the-counter products. Especially often, these are dietary supplements of vegetable origin. Considering the risk of adverse drug interactions between them is an integral part of conducting effective pharmacotherapy in a patient's bed. In the dissertation presented, contemporary approaches to assessing the risk of adverse drug interactions are convincingly demonstrated.

The work is written on a total of 320 pages. It is structured appropriately in 7 separate sections, designated as chapters. Literary review at the beginning of work - Chapter I, becomes particularly important as a theoretical basis for the study. It reflects objectively the current state of knowledge in the field of molecular mechanisms of drug interactions.

The specific features of the study of the selection, isolation and analysis of plant extracts and their fractions of plants of Goji berry (Lycium barbaricum) and tea leaves (Camellia sinnensis) are shown. They are one of

the most widely used nutritional supplements, both in Bulgaria and globally.

The design, synthesis and analysis of novel synthetic oligopeptides derived from endorphin-2 and RGD are presented in a stand-alone section. The pharmacokinetic and pharmacodynamic mechanisms of drug interactions of the investigated medicinal products are presented in the same way. These sections of the dissertation are structured according to the classical scheme: the purpose of the research, research methods, results, discussion.

Of particular interest is the retrospective study of the risk of adverse drug interactions in clinical practice.

In this way, the dissertation acquires a monographic structure that is objectively imposed by the many different methodological approaches used in the various chapters. The monographic organization of the dissertation is highly appreciated. It undoubtedly contributes to his understanding.

The purpose of the dissertation is clearly and precisely stated.

Solving the tasks that are set ensures that the goal is achieved.

An impressive set of methodological approaches, including liquid chromatographic techniques, the use of screening kits to determine the enzymatic activity of cytochromes of the P 450 group, software simulation systems, classical biochemical and histopathological techniques, and advanced computer processing have been used to accomplish these tasks. The studies were performed both in vitro and in vivo in experimental animals. The methodological richness of the dissertation is impressive and worthy of appreciation.

The reliability of the results of the study of the risk of adverse drug interactions of plant products is directly dependent on the selection, isolation and chemical analysis of the plant extracts.

Of particular interest in this regard are the studies conducted on the Goji berry plant. Three fractions were isolated from it: total extract, safecin fraction and polysaccharide fraction. The antioxidant activity of the plant is

the leading in its use as a medicinal product. It is found in all three fractions, but is best correlated with the saftin fraction and the content of polyphenols in it. It is this fraction that is used to determine the risk of adverse drug interactions.

The determination of the methylxanthine components of Pu-er tea extracts, which determine its biological activity, is also beneficial.

The pharmacokinetic and pharmacodynamic mechanisms of drug interactions are crucial for their understanding, both theoretically and clinically. The section of the dissertation on pharmacokinetic drug interactions occupies a central place in volume - over 100 pages, and in importance. It competently discusses aspects of the problem of fundamental importance. The methodological approaches for controlling the metabolism of medicinal products with the participation of the two major drug-metabolizing enzymes of the cytochrome CYP 450, CYP3A4 and CYP2C9 group are presented in detail. A wide range of advanced computerized hardware technologies are used, including simulation systems and predictive sophisticated models and products. Of interest are the described approaches for predicting changes in basic pharmacokinetic parameters such as absorption, distribution, and elimination. The techniques are very well presented and demonstrate a thorough theoretical background for the dissertation.

From a clinical and theoretical point of view, the established inhibition of drugs is the metabolic enzymes under the influence of methylxanthines isolated from Puer and Bancha teas. It is larger than that of caffeine. The difference is limited in size and does not limit the use of teas at the same time as medicinal products metabolised with the participation of CYP 3A4.

Of interest is the established inhibitory effect on the surfactin fraction of CYP 3A4 and CYP 2C9 from Goji Berry extract. This requires caution when co-administering medicinal products that are metabolised with the participation of these enzymes and extracts from Goji berry. This requires caution when co-administering medicinal products that are metabolized with the participation of these enzymes and extracts from Goji berry.

The newly synthesized compounds, which are analogues of endorphin-2 and REG, have antitumor and analgesic activity. The study of cytochrome CYP 3A4 inhibitory compounds does not warrant a restriction on their future combination with other medicinal products metabolized by its involvement. These data are of interest in view of their possible future entry into therapeutic practice.

Studies on the pharmacodynamic mechanisms of drug interactions are aimed at determining the effects of selected plant fractions on neoplastic tissues and the risk of adverse reactions and their occurrence, when co-administered with widely used antineoplastic medicinal products and specifically with doxiru. The established effects of selected plant fractions on the risk of cardiotoxicity and nephrotoxicity in doxorubicin treatment is of considerable interest in oncology practice.

The studies were performed in vitro on healthy and neoplastic cell lines, as well as in vivo on Wistar rats. The selection of cell lines used and the approaches to assess their vitality are thoroughly selected. The design of the experimental study is very well prepared and includes biochemical analyzes, histopathological controls of the heart and kidneys and highly informative statistical processing. Of particular interest is the established antiproliferative effect of methylxanthine fractions isolated from Bancha and Puer teas. Methylxanthines isolated from Bancha tea have a synergistic effect when combined with doxyrubicin on a breast cancer cell line. They also established a cardio- and nephro-protective effect of doxrubicin-induced cardio and nephrotoxicity. These data allow the combination of Bancha tea with doxyrubicin to be considered appropriate. A synergistic effect with doxyrubicin was also found when combined with a safcin and polysaccharide fraction of Goji berry in human breast cancer cells. The two fractions, each alone and in combination, exhibit cardio- and nephro-protective activity in a doxrubinin-induced cardio- and nephro-toxicity model. As with the methylxanthine fractions of Puer and Bancha in the treatment of breast cancer. They can be combined, given the combination of enhanced antitumor activity with reduced dose-dependent cardio- and nephrotoxicity.

Of particular interest and appreciation is the section of the dissertation on "Study and analysis of pharmacokinetic and pharmacodynamic drug interactions in clinical practice". It reflects the results of a retrospective study of the risk of drug interactions, according to the documentation of the Cardiology Clinic at the University Hospital "St. Marina "- Varna on the impressive total number of 1956 patients for a period of 2 years (2014 - 2015). Of these, 487 were classified as at risk of drug interactions. The criteria for this selection are very well selected and determine the high informative value of the study. It is largely determined by the proper selection of risk factors. These are: the magnitude of the risk, the severity of the adverse reaction, the result of the pharmacokinetic computer simulation, the demographic characteristics of the patient, the limited therapeutic breadth of the drugs included in the therapy, such as statins, anticoagulants, antithrombotic agents, etc. Particular attention is paid to the use of cardiac glycosides.

The use of computer simulation of drug interactions should be specifically noted. For example, it makes it possible to determine the magnitude of the risk when co-administered with small therapeutic width drugs and drugs that inhibit the activity of cytochrome group enzymes.

Particular attention in the dissertation is devoted to computer technologies in the definition, analysis and evaluation of drug interactions. This makes it a valuable tool for those working in the field.

The results obtained are convincingly presented in the form of tables, figures and photographs.

Discussion of the results obtained is thorough and competent. It not only provides an overall assessment of the research conducted, but also outlines the current directions for future research in this area.

The conclusions of the study are very well formulated and objectively reflect the results obtained.

The assessment of the dissertation by the dissertation on the results of a contributory character in the dissertation is objective.

Literary reference covers a total of 440 sources. They are presented separately after each chapter of the dissertation.

The abstract objectively reflects the essence of the dissertation.

In connection with the dissertation, the dissertation has a total of 19 publications. Of these, 11 have been published in the last two years.

CONCLUSION

The dissertation presented makes a significant contribution to the understanding of the mechanism and risk assessment of drug interactions. The contribution to the methodological approaches in the conducted studies is inextricably linked to the use of modern computer-computing techniques. The relevance of these studies is demonstrated at all stages of drug design and administration: from in vitro studies, experimental in vivo animal studies, to clinical observations and bedside studies.

The dissertation work "Identification, analysis and evaluation of pharmacokinetic and pharmacodynamic drug interactions" fully meets the approved regulatory requirements for the award of its author **Assoc. Prof., mag. pharm., Kaloyan Dobrinov Georgiev, Ph.D., the scientific degree "Doctor of Sciences".**

Sofia, February 14, 2020

Prof. Dr. Vitan Dakov Vlahov - Ph.D.