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National Research Programme "Innovative Low-Toxic Bioactive Systems for Precision Medicine (BioActiveMed)"

The **National Research Programme *"Innovative Low-Toxic Bioactive Systems for Precision Medicine (BioActiveMed)"*** was approved by DCM №658/14.09.2018 and is performed on the basis of a signed agreement Grant DO1-217/30.11.2018 between Ministry of Education and Science and Bulgarian Academy of Sciences (BAS). A prerequisite for the implementation of the NRP BioActiveMed is the fact that Bulgaria, with its unique climatic and ecological factors, offers an amazing variety of plant and animal species. Isolated extracts contain a series of bioactive compounds that resembles combined therapy with several synthetic compounds. It is well known that extracts from natural products are less toxic than synthetic and are better tolerated by the human body. Therefore, the proposed in the Programme approach is one of the key to overcoming multiple drug resistance.

The Programme is focused on the development of new low toxic bioactive substances and systems containing extracts of natural sources (of plant or animal origin) from Bulgaria for the prevention and support of the therapy of certain diseases. The first step is the isolation and purification of bioactive substances of plant and animal origin, their appropriate incorporation in suitable innovative systems and development of new methodologies for their characterization and determination of quality and applicability as new products in personalized and preventative medicine. One of the planned long-term applications is the implementation of new innovative healthy and safe food supplements and cosmetics with a preventive potential for personalized medicine.

The research has been carried out with the participation of leading scientists with proven scientific capacity, as well as with the active participation of young scientists and PhD students from the Consortium formed. The leading organization is the Bulgarian Academy of Sciences and the following scientific organizations (seven scientific units from the BAS) and higher education organizations with the highest capacity in the field of the Programme are Partners: Institute of Organic Chemistry with Center of Phytochemistry (Partner 1), Institute of Molecular Biology (Partner 2), Institute of Microbiology (Partner 3), Institute of Neurobiology (Partner 4), Institute of Experimental Morphology, Pathology and Anthropology with Museum (Partner 5), Institute of Polymers (Partner 6), Institute of Information and Communication Technologies (Partner 7), Medical University – Sofia (Partner 8), Sofia University "St. Kliment Ohridski" (Partner 9), Medical University – Plovdiv (Partner 10), Plovdiv University "Paisii Hilendarski" (Partner 11) and National Sports Academy "Vasil Levski" (Partner 12).

The research activities are divided in the following **8 work packages (WPs)**:

Work package 1 (WP 1). Preparation of novel bioactive substances/systems containing extracts of natural sources (of plant or animal origin) from Bulgaria.

WP Leader Prof. DSc Pavlina Dolashka

The aim of the WP 1 is to isolate and purify bioactive substances (BASs) of plant or animal origin and to incorporate them into appropriate innovative systems. Isolated individual BASs or obtained innovative systems will used for preparation of innovative products for potential applicability to improve human health. It is also envisaged to characterize in details the structure and properties of the BASs in order to explain their mechanism of action. The following Bulgarian plant and animal species will be studied:

Ginkgo biloba seeds

Tamus communis L.

Betonica bulgarica

Salvia

Nepeta nuda

Thymus

Gentiana

Helix aspersa

Rapana venosa

Work package 2 (WP 2). Investigation of the anti-infective potential of the obtained low-toxic bioactive BASs/systems.

WP Leader Prof. Dr. Svetlozara Petkova

The purpose of the WP 2 is to evaluate the antifungal activity of the obtained low-toxic bioactive BASs/systems containing extracts of Bulgarian natural sources (of plant or animal origin) on fungal strains, as well as their antiparasitic and antiviral activity. The antifungal potential and determination of the inhibition dose will be carried out against *Aspergillus, Mucor, Penicillium, Cladosporium, Fusarium, Alternaria, Botrytis sp*. Studies will also be provided on an *in vivo* parasitic model of *Trichinella*, as well as on a model of sleeping sickness (*African trypanosomiasis*). In addition, the first and second types of Human Herpes Virus will be used as viral models.

Work package 3 (WP 3). Investigation of the obtained low-toxic bioactive BASs/systems on bacterial in vitro systems.

WP Leader Prof. DSc. Hristo Najdenski, DVM, Corr. Member of BAS

WP3 will study the antibacterial activity of the obtained bioactive BASs/systems containing extracts of natural sources (of plant or animal origin) against Gram(+) and Gram(–) bacteria, which are high-risk pathogens and have developed multiple drug resistance. The use of the following microorganisms is envisaged, according to the ISO 20776-1:2006: *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 35218, *S. aureus* NBIMCC 3359, *S. aureus* ATCC 3865 P, *S. aureus* NBIMCC 8327, *S. epidermidis* NBIMCC 1093, B. *cereus* ATCC 9634 and *Candida albicans* SAIMC 562I.

Work package 4 (WP 4). *In vitro* and *in vivo* study of the effectiveness of the obtained low-toxic bioactive BASs/systems against neurodegenerative diseases.

WP Leader Prof. Dr. Lyubka Tancheva

This WP aims to study *in vitro* neurotoxicity of the obtained BASs/systems and *in vitro* activity onto models of Alzheimer's disease (AD) and Parkinson's disease (PD), as well. *In vivo* efficacy of the obtained innovative BASs/systems on the impaired cognitive and motor functions of experimental animals with an experimental model of AD and PD will also be studied.

Work package 5 (WP 5). Study of the antitumor activity of the obtained low-toxic bioactive BASs/systems.

WP Leader Prof. Dr. Iva Ugrinova

The studies in this WP are focused on *in vitro* study of the antineoplastic activity of the isolated extracts and obtained BASs/systems in models of malignant diseases. Several cancer models will be used – three lung cell lines MRC-5, A549 and H1299, three lines of breast cancer MCF-10A, MCF-7 and MDA-MB-231, and two lines of cervical cancer HeLa and Wish. Malignant-transformed skin T-cell lymphoma cell lines will also be used (CTCL) – MJ (ATCC № CRL-8294) and HuT-78 (ATCC № TIB-161TM, ECACC № 88041901), as well as bladder cancer cells T-24

(DSMZ№ ACC 376), SW-1710 (DSMZ № ACC 426) и CAL-29 (DSMZ№ ACC 515).

Work package 6 (WP 6). Modeling, prognosis and modulation of the therapeutic effect of BASs through a theoretical, computational and experimental methods and techniques.

WP Leader Prof. Dr. Nevena Ilieva-Litova

This WP aims to identify potential biotherapists in peptide mixtures of natural origin as a basis for alternative approaches for treatment of the infectious diseases caused by multidrug-resistant bacterial strains and in immunocompromised patients. An *in silico* studies of the behavior in solution of isolated peptides in mono- and multipeptide compositions will also be performed.

Work package 7 (WP 7). Study of the applicability of the obtained low-toxic bioactive BASs/systems in the biopharmaceutical industry.

WP Leader Prof. DSc. Spiro Konstantinov, MD

The work package is focused on study of the applicability of the obtained low-toxic bioactive BASs/systems as food supplements or cosmetics in terms of genotoxicity, carcinogenicity, mutagenicity and teratogenicity, as well as the development of innovative systems for the supply of low-toxic extracts/BASs, ensuring optimal bioavailability after oral or local administration.

Work package 8 (WP 8). Development of innovative food supplements and cosmetics for local application with preventive potential for personalized medicine.

WP Leader Prof. Dr. Stoyan Shishkov

This package aims to develop end products as innovative food supplements and cosmetics for local application with preventive potential. The main object of the WP is to select the most effective BASs/systems for incorporation in food supplements or cosmetics.

More information can be found on the web page of the Programme: www.bioactivemed-nrp.com.

Prof. PhD Olya Stoilova

Bulgarian Academy of Sciences, 1040 Sofia, 15th November 1, str.; E-mail: olya.stoilova@cu.bas.bg