МЕДИЦИНСКИ УНИВЕРСИТЕТ - ВАРНА
„Проф. д-р Параскев Стоянов“
Ул.“Марин Дринов“ 55, Варна 9002, България
Тел. : 052/ 65 00 57, Факс: 052/ 65 00 19
e-mail: uni@mu-varna.bg, www.mu-varna.bg

MEDICAL UNIVERSITY - VARNA
“Prof. Dr. Paraskev Stoyanov”
55, Marin Drinov Str., 9002 Varna, Bulgaria
Tel.: +359 52/ 65 00 57, Fax: + 359 52/ 65 00 19
e-mail: uni@mu-varna.bg, www.mu-varna.bg

Fund “Nauka” Project № 18027 Resume – Competition-Based Session 2018:

“Lipid nanoparticles – a modern technological approach for inclusion of hyperforin with improved chemical stability in topical formulations for accelerated wound healing”

Project leader: Assoc. prof. Velichka Yordanova Andonova, PhD

St. John's wort (*Hypericum perforatum L.* - Hypericaceae) is a plant with a proven place in ethnopharmacology. Modern methods for qualitative and quantitative analysis prove the content of a rich palette of biologically active substances (BAS), which, along with anxiolytic and antidepressant properties, show antioxidant, anti-inflammatory, regenerative, antibacterial, and immunostimulatory effects. It has been established that the main carriers of these characteristics are the contained hypericin and hyperforin. The photosensitivity and phototoxicity of the plant extract have also been shown to be due to hypericin. The focus of the present project is on hyperforin – a bicyclic polyprenylated acylfloroglucinol derivative, which in addition to the above-mentioned biological effects, has a pronounced protective (UV-VIS and IR) effect after topical application, and taken orally does not cause any photosensitivity.

Hyperforin is characterized by relatively low stability to oxygen and light exposure, and poor solubility in water. The use of nanoscale BAS carriers can overcome these disadvantages, as solid lipid nanoparticles (SLNs) and the next class of nanostructured lipid carriers (NLC) are characterized by indisputable biocompatibility, biodegradability, and lack of toxicity.

The aim of the present project is to study the wound-healing effect of hyperforin, extracted from St. John's wort and incorporated into emulgel and bigel (topical semi-solid dosage forms), in the form of SLN and NLC as a modern approach to chemical stabilization of BAS. The project proposal is comprehensive and interdisciplinary in nature, starting with the isolation of hyperforin from plant material, with its subsequent standardization, stabilization through its incorporation into nanoparticles, formulation of dosage forms (emulgel and bigel), and evaluation of wound healing effect after their application.

Obtained results:

The main objective of this project is the investigation of the wound-healing effect of hyperforin contained in St. John's wort. For this purpose, an extract of St. John’s wort, rich in hyperforin, was initially obtained. The phytochemical, however, is characterized by very low stability when exposed to oxygen and light. A successful protective approach is to incorporate the extract into a suitable drug delivery system. Regarding the lipophilic nature of hyperforin,

various lipid-based platforms were investigated, and lipid nanoparticles were selected as the most suitable ones. After detailed literature research concerning lipid nanoparticles, their main characteristics, composition, advantages and disadvantages, preparation methods, and proven contributions of their use in wound healing are summarized.

Different models of nanostructured lipid carriers were developed, and those presenting favorable properties were loaded with the hyperforin-rich St. John's wort extract. After detailed characterization, the optimal carrier is gelled to serve as the hydrophilic phase of the bigel. Eight bigels with different proportions of hydro- and oleogel (empty and loaded with nanodispersion) are prepared. They are characterized rheologically and texturally to investigate the effect of the hydrogel-to-oleogel ratio as well as the effect of the incorporated nanodispersion. The therapeutic potential of the superior formulation is evaluated in vivo on male Wistar rats by performing a tensile strength test on a primary healed incision wound. Compared to a commercial herbal product and a control, untreated group, the highest tear resistance is achieved after the application of bigel containing the nanoencapsulated extract, proving its superb wound-healing effect.

Hyperforin toxicity is investigated in silico and in vivo. The computational analysis predicts low risk due to the inability of acylphloroglucinol to bind to DNA and/or proteins, but structural signals for skin irritation, carcinogenicity, and mutagenicity were found. In order to evaluate the possible organ toxicity, in vivo experiments are performed on Wistar rats by treating excisional wounds with bigels containing "free" and nanoencapsulated extract. Their effects after 2-, 7-, 14-, and 21-day administration are compared with positive (animals treated with a commercial herbal product) and negative (untreated rats) controls. A beneficial effect on free radical scavenging capacity and the degree of liver/tissue damage is found. The promising results obtained after the administration of the biphasic gel containing nanoencapsulated St. John's wort extract suggest that the drug delivery system used could not only effectively stabilize hyperforin but also unfold its cyto- and hepatoprotective potential.