

## **Cannabidiol as a potential therapeutic agent for psoriasis and its role in the stabilization of physiological level of lipid mediators**

Psoriasis is a disease associated with increased proliferation and death of epidermal cells – keratinocytes. It is known, that the psoriasis development depends on genetic and environmental factors such as stress, infections and xenobiotics. Therefore psoriatic lesions are a growing concern for health, but also psycho-social among people of all ages (it is estimated that this disease occurs in 1 per 25 people). The prevalence of psoriasis, its long duration and the tendency to relapse lead to accurate analysis of the changes in metabolism responsible for psoriasis development. Ultimately, it could help in the elaboration of a new, effective and targeted therapies.

The development of psoriasis is accompanied by long-term whole-body inflammatory response and oxidative stress appearing in skin cells, resulting in oxidative modifications mainly of lipids, proteins and DNA in keratinocytes. Modifications of these molecules structure mostly change also their functions. Due to the large variety of functions in skin cells, particularly important molecules are lipids, which are basically composed of fatty acids. Enzymatic and free radical metabolism of fatty acids leads to the formation of lipid mediators belonging to the following groups: products of lipid peroxidation, endocannabinoids, eicosanoids and sphingolipids. All these molecules are involved in intra- and intercellular signal transduction system. The final products of lipid peroxidation - reactive aldehydes modify the structure of intracellular and membrane proteins, while cyclization products can be exchanged between adjacent cells or be released into the bloodstream, spreading information about the cells condition throughout the organism. Modifications of protein structure cause disturbances in the physiological processes of signal transduction, gene transcription or proteasomal degradation, which may lead to excessive proliferation and apoptosis of keratinocytes. Also oxidative DNA damages affect the replication intensity and may change the structure and activity of newly synthesized proteins. However enzymatic fatty acids transformation leads to endocannabinoids, sphingolipids and eicosanoids generation. The biological activity of these compounds is accomplished by regulating a number of skin cells functions, such as proliferation, survival, oxidative stress and immune response. Eicosanoids play a key role in the regulation of inflammatory processes, mainly through the inhibition of the arachidonic acid metabolism, however, they also participate in the collagen biosynthesis. Sphingolipids, despite of the structural function in the cell membrane, are involved in cellular metabolism and as signal molecules regulate cell growth and proliferation, apoptosis, angiogenesis and inflammation. So far, it is not known the rate of changes occurring in the level of these lipid mediators in the case of psoriasis and which of them are particularly responsible for the formation of the development of this disease. However, it is known that one of the main endocannabinoids – anandamide, inhibits the differentiation of keratinocytes and participates in inflammatory response suppression. Therefore, it may be expected that manipulating the levels of endocannabinoids by supplementation with exogenous cannabinoids will restore the physiological conditions in psoriatic patients. An example of an exogenous fitocannabinoid which does not cause psychoactive effect is cannabidiol. It is a natural compound which has anti-inflammatory and antioxidant properties, and may be a potential inhibitor of keratinocyte proliferation process. Moreover, because of its lipophilic nature it is easily absorbed by the skin, which simultaneously nourishes that is also important in the case of psoriasis. Thus, from the academic and social point of view it is significant to check the potentially pharmacological effect of cannabidiol in psoriasis.

Therefore, this project will include analysis of the composition and level of lipid mediators in a context of changing parameters related to antioxidant activity, immune response, and intracellular signals transduction. Also the changes in proteomic and lipidomic profile of skin cells (responsible for psoriasis lesions – keratinocytes, and adjacent with them – fibroblasts) isolated from psoriatic patients will be defined. Moreover, the modification of the components of above systems in the plasma and blood immune cells will be assessed including neutrophils ability to create a neutrophil-cellular network (NET's) associated with a unique form of cell death known as NET-osis. Simultaneously, also research on the ability of cannabidiol to stabilize the physiological level of lipid mediators as a consequence of the interactions between the redox and immunological systems and pro-inflammatory parameters in cells cultured *in vitro* and in animal studies will be conducted.