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Review

of the doctoral dissertation of MSc Sinemyiz Atalay Ekiner

" Protective effects of cannabidiol on skin keratinocytes in an oxidative microcellular environment induced by UVA/B radiation or exposure to hydrogen peroxide "

Dissertation for a doctoral degree in the medical and health sciences in the discipline of pharmaceutical sciences.

The assessment was prepared based on materials provided by the College of Pharmaceutical Sciences of the Medical University of Bialystok based on Resolution No. 157/2022 of the Senate on April 28, 2022.

Introduction

The work delivered to me for review was carried out under the scientific supervision of two supervisors, i.e., Prof. dr hab. Elżbieta Skrzydlewska from the Department of Inorganic and Analytical Chemistry of the Medical University of Białystok and Prof. dr hab. Pedro Domingues from the Department of Chemistry, University of Aveiro, Portugal.

1. The importance of the research

The subject of the work concerns an important and current problem of exposure to oxidative stress and UV radiation, which may contribute to the induction of DNA damage, inflammatory processes, and disorders of cell metabolism. The Ph.D. student evaluated the role of cannabidiol (CBD) in the metabolism of keratinocytes in the context of the response to factors inducing oxidative stress, i.e., hydrogen peroxide (H_2O_2) and UV radiation. Both extracellular stressors

are widely used in dental practice. Therefore the undertaking of the topic and the selection of the model and methodology are justified and well documented. The process of research planning and presentation of results is straightforward. The issue of intracellular homeostasis is a very important topic in the context of metabolic disorders, including those underlying carcinogenesis. The selection of the research model, i.e., keratinocytes, was essential, especially referring to the composition of their cell membranes (phospholipids and proteins). Particular publications constitute an attempt to identify the role of cannabidiol in the mechanisms related to oxidative stress. Thus, the first paper deals with the antioxidant and anti-inflammatory potential of the studied compound. In another, the author examines the role of CBD in maintaining the redox balance in the cell. The following work is the evaluation of the role of hydrogen peroxide in the modulation of the keratinocyte proteome. Further work is focused on i) the importance of CBD for the modulation of the proteome of keratinocytes exposed to UVB, the pro-apoptotic effect of CBD and its involvement in the processes of translation, proliferation, and redox equilibrium, and ii) the role of CBD in the response observed *in vivo* in rats exposed to UVB - here the author attempted to analyze the protein profile and apoptosis.

2. Evaluation of the work

A) Substantive assessment

The author precisely defined the assumptions and purpose of the work and consistently pursued their implementation. Indeed, the strength of the work is the extensive multivariate analysis with the use of modern molecular methods and appropriate statistical tools. The doctoral student analyzed the consequences of exposure of eukaryotic cells to UVB and H_2O_2 in the context of redox system disorders, referring her research to the literature of the last few years. She performed a detailed analysis of the protein and lipid composition of the keratinocyte cell membrane and attempted to explain the mechanism accompanying exposure to the indicated stressors. Her research also related to the proteasomes and the integrity of the cell membranes in the context of the protective effect of CBD. The presented analysis is multidirectional and indicates both favorable and unfavorable effects of CBD in the studied biological model. The carried out research and the obtained results led the Ph.D. student to the formulation of five main conclusions. The study and the works are very efficiently written, and discussions are conducted carefully regarding the latest literature. The summary lacks only a commentary on the potential use of the results in practice, and in the opinion of the reviewer, this part should

be more clearly emphasized. However, the implementation aspect was raised in individual publications.

B) The formal side

The dissertation was prepared very carefully using standard recommendations. The cited literature is extensive, mainly from recent years. Two abstracts in Polish and English summarize the work. The work contains relevant statements from all co-authors, which, it is worth emphasizing, are few. The contribution of the doctoral student to all papers is estimated as at least 60%. An integral part of the work is the consent of the bioethical committee regarding *in vivo* studies in rats (Olsztyn).

C) Notes for work

Even though the work is very valuable, there is still a lack of consideration for differences in pharmacogenetics, pharmacogenomics, and genetic profiling in terms of SNP, methylation, etc. It is undoubtedly a valuable area that can lead to more effective and personalized approach to the patient.

It is also worth mentioning that rats (the *in vivo* research model) are characterized by a slightly different mechanism of reaction to stress than humans - corticosterone (in rats) is of greater importance in this process than cortisol (in humans).

Although indeed high, the IF factors for publications 1, 3, and 5 have been overestimated concerning the publication years.

There is no reference to other antioxidants, apart from some minor ones in the publications. Probably the bioinformatics analysis allowing the assessment of docking could bring a lot beneficial information.

There was also a lack of a clearer vision for future research. It would also be worth considering the H_2O_2 stability.

3. Conclusion

The doctoral student raises a critical and exciting topic in her dissertation. The method of presenting the obtained results is transparent, and the papers constituting the basis of the dissertation are of excellent quality. After reading the doctoral dissertation, I can say that the author has prepared an exciting and valuable dissertation.

The work presented to me for review by MSc Sinemyiz Atalay Ekiner entitled: "Protective effects of cannabidiol on skin keratinocytes in an oxidative microcellular environment induced

by UVA / B radiation or exposure to hydrogen peroxide" fully corresponds to the requirements of the doctoral degree specified in the Regulation of the Minister of Science and Higher Education of January 19, 2018, on the detailed procedure and conditions for carrying out activities in the doctoral thesis, in the habilitation proceedings and the procedure for awarding the title of professor (Journal of Laws of 2018, item 261).

The above conclusions authorize me to apply to the College of Pharmaceutical Sciences of the Medical University of Bialystok for admission of Sinemyiz Atalay Ekiner to further stages of the doctoral dissertation.

At the same time, due to the very high value of the observations made and the publication of the results in very good journals, I am applying for the dissertation to be distinguished.

Yours faithfully,

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