Maastricht, July 2018

Evaluation of the PhD thesis of Agnieszka Gęgotek entitled ‘Effect of rutin on metabolic changes in skin cells exposed to UVA and UVB radiation’. The PhD is written in the field of pharmaceutical sciences within the Faculty of Pharmacy, the Division of Laboratory Medicine.

After a short introduction (**chapter 1**) on UV radiation and oxidative stress, the effect of UV on the nrf2 system and the description of the flavonoid rutin, the aims of the thesis have been described in **chapter 2**.

The first aim was to determine the effect of UVA and UVB radiation on skin cells (*i.e.* keratinocytes and fibroblasts) with a certain focus on effects on redox balance and related changes in cellular homeostasis. The second aim was to determine the effect of plant-derived flavonoid rutin in these effects of UVA and UVB.

**Chapter 3** gives a nice and concise overview on the role of the nrf2 system in skin cells. It is concluded that nrf2 in keratinocytes and melanocytes protects against mutations which might occur during keratinization and melanogenesis. In fibroblasts nrf2 plays a role in differentiation and proliferation and thus in wound healing and inflammation. The overview with the candidate as first author is published in Arch. Dermatol. Res.

**Chapter 4** describes ‘the cross-talk between electrophiles, antioxidant defense and the cannabinoid system in fibroblasts and keratinocytes after UVA and UVB irradiation’. An impressive variety of methods has been employed in this chapter: measurement of enzymatic and non-enzymatic antioxidants, various oxidative damage parameters, bioimaging, western blotting etc. The obtained data ‘open new avenues for therapy in dermatology’ as I might paraphrase the statement by the authors. This chapter was published in J. Dermatol. Sci.

Investigations as described in **chapter 5** on the effect of rutin (*i.e.* the second aim of the thesis) formed the basis of a beautiful paper in the high ranking journal Redox Biology. The candidate has to be congratulated with this nice paper. Again a multitude of techniques and methods have been employed to reach the conclusions of the paper that rutin is an effective protector of skin cells against UV irradiation. More specifically, rutin positively changed the redox balance in fibroblasts as measured in the cytosol (uptake via bilitranslocase) and in the membrane (phospholipid levels).

**Chapter 6** entitled ‘Rutin as mediator of lipid metabolism and cellular signaling pathways interaction in fibroblasts altered by UVA and UVB radiation’, provides more details on the effect of rutin on fibroblasts. The protective effect of rutin has now been investigated at a protein and transcriptional level. Of course after reading various chapters one becomes used to the usage of the variety of methods used by the candidate, however this remains quite impressive. The chapter was based on a publication in Oxidat. Med. Cell. Longevity.

A proteomic approach has been used (in **chapter 7**) to further delineate the effect of rutin in combination with UV radiation in dermal fibroblasts. The data have been published in J. Dermatol. Sci. and is entitled ‘Proteins involved in the antioxidant and inflammatory response in rutin-treated human skin fibroblasts exposed to UVA or UVB irradiation.

**Chapter 8** gives a nicely readable overarching and illustrated discussion of the obtained data. **Chapter 9** provides the enumerated conclusions of the thesis. The summary of **chapter 10** is followed by the list of publications (**chapter 11**) that formed the basis of the thesis.

In conclusion, I am very impressed by the quality of the thesis. In particular the multitude of techniques and methods used by the candidate is extraordinary. Moreover, all the results have been published in good and even very high ranking journals like Redox Biol. with an impact factor of 6.3. The total impact factor aggregate is well above 8. It is therefore without any hesitation that I would like to propose to award the distinction to this doctoral thesis.

Prof. dr. A. Bast