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Evaluation of the PhD thesis of **Andrzej PATYRA** entitled « Effets et mécanisme d'action de métabolites secondaires des plantes sur la régulation de la sécrétion d'insuline »

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The dissertation of Andrzej Patyra entitled « Effets et mécanisme d'action de métabolites secondaires des plantes sur la régulation de la sécrétion d'insuline » reports his pre-clinical research conducted under the co-direction of Professor Catherine Oiry-Cuq at the "Institut des Biomolécules Max Mousseron" of the University of Montpellier, France and Professor Anna Karolina Kiss at the Department of Pharmaceutical Biology, Faculty of Pharmacy of the Medical University of Warsaw, Poland.

Treatment of type 2 diabetes remains a major challenge since the number of diabetic patients is still on the rise and the current antidiabetic pharmacological treatments despite reducing effectively chronic hyperglycemia can be associated with major adverse events including hypoglycemia, lactic acidosis, gastrointestinal side effects, and urinary infections. Moreover, type 2 diabetes is now considered as a cardiovascular disease characterized by alteration of the function of both macro and microvascular blood vessels that can lead to severe cardiovascular events including coronary artery syndrome and stroke. Thus, novel improved antidiabetic treatments are crucially warranted to provide greater health benefit for type 2 diabetes patients.

For this purpose, the research project of Andrzej Patyra aims to search for innovative antidiabetic compounds from different sources of natural products, to characterize the phytochemical composition and in particular flavonoids, lignans and coumarins, to evaluate their ability to modulate the beta-cell function and in particular the secretion of insulin in a glucose-dependent manner, and to characterize the involved mechanisms such as those regulating the insulin secretion process.

The research project is highly original, ambitious, and extremely challenging. Indeed, even though natural products can provide highly creative and often complex chemical molecules, phytochemical compounds in plants and fruits are often complex mixtures of a high number of compounds often conjugated and with numerous compounds that have not been identified. Nevertheless, M Patyra carefully selected a group of natural products based on the literature and experience of both teams, prepared extracts, fractionated the extracts to isolate individual compounds and characterized their structure. This was a huge amount of work and M Patyra should be congratulated for this investment which led to the identification of interesting compounds including flavonoids, lignans and coumarins.

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In a second step, M Patyra evaluated the ability of the natural compounds (the obtained metabolite libraries, and pure compounds) to modulate the secretion of insulin in a glucose-dependent manner and to have protective effects of beta cells using a cell line INS-1. Of interest, the study of a high number of closely related phytochemical compounds provided interesting information regarding key elements of the structure required for insulin secretion.

In a third step, M Patyra aimed to unravel mechanisms underlying the modulatory activity of active compounds by assessing their effects on several key regulatory mechanism of insulin secretion such as the activator calcium signal, cell electrical activity and trace currents of calcium and potential.

Altogether, the thesis is well structured, written, and easy to follow. The introduction is of high quality and provides the different elements to understand the rational of the experimental investigations. The experiments have been well planned and performed, and the data are analyzed and presented in a professional manner to highlight the significant effects. A great effort has been made to unravel not only active compounds but also to characterize the active pharmacophore and to decipher underlying mechanisms using a batterie of sophisticated experimental approaches. The interesting observations of M Patyra have already been appreciated by the scientific community with 3 published papers as first author, one in review as co-author, and 4 which are ready for submission (3 as first author). He is also listing 5 additional papers (1 as first author), 11 communications at scientific conferences as first author, and several awards.

In conclusion, the present study provides clear experimental evidence of promising natural compounds for the treatment of type 2 diabetes. Based on the high quality of the research and thesis document as well as the incredible amount of work and data collected, I would like to strongly recommend acceptance of the thesis for PhD degree.

Sincerely yours,



Professor V. Schini-Kerth

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