

HABILITATION THESIS REVIEWER'S REPORT

Masaryk University

Applicant

PharmDr. Jakub Tremel, Ph.D.

Habilitation thesis

Natural phenolics in alleviation of symptoms and complications of type 2 diabetes mellitus

Reviewer

Prof. MUDr. Iva Slaninová, Ph.D.

Reviewer's home unit, institution

Masaryk University, Faculty of Medicine, Department of Biology

The habilitation thesis submitted by Dr. Jakub Tremel represents a comprehensive and thematically coherent scientific work focused on the biological activity of natural phenolic compounds in the context of type 2 diabetes mellitus (T2DM). This thesis is a collection of 12 peer-reviewed papers published between 2010 and 2025. The work is focused on the antioxidant (five papers), anti-inflammatory (two papers) and antidiabetic (two papers) effects of these compounds. Three papers describe the effect of encapsulation of the phenolics on their solubility and biological activity. Dr. Tremel is the first author of the seven and the corresponding author of one of these papers. The total impact factor of the articles is 59.264. Dr. Tremel's contribution to these publications is substantial, often leading the manuscript preparation and conceptual direction.

The aim of the projects included in the thesis was to identify compounds that may contribute to the decreasing of hyperglycemia and T2DM complications. The introduction focuses very briefly on the issue of T2DM and, generally and briefly, on the history and significance of natural products in medicine. Substantial part of the introduction is devoted to describing the structure of the habilitation thesis and the author's contribution to the included publications. Given that the author is the head of the Department of Molecular Pharmacology, attention is also paid to the importance of this field. More detailed information on T2DM is provided in Chapter 2. Chapter 3 focuses primarily on describing the studied compounds and summary of experimental methods and findings. The results are summarized in the Conclusions chapter. This is followed by References, which include 82 citations, and the full text of 12 author articles. The habilitation thesis presents a scientifically grounded exploration of natural phenolic compounds with potential therapeutic applications in T2DM. The thesis is distinguished by its original approach to combining three therapeutic effects, antioxidant, anti-inflammatory, and antidiabetic within a single compound. The experimental design is well-justified, the author employs a wide range of biochemical and biological experimental techniques, including antioxidant, anti-inflammatory and antidiabetic assays. I greatly appreciate that the thesis also addresses the challenge of poor bioavailability of phenolic compounds by exploring encapsulation techniques (glucan particles; cyclodextrins, liposomes). The results are interpreted with appropriate caution and scientific insight. The author identified diplacone, a geranylated flavanone, as a model compound exhibiting all three activities. Additional compounds such as diplacol and moracin M were also highlighted for their promising biological effects.

The originality of the work lies in the systematic evaluation of several natural compounds, using a variety of experimental models and in the proposal of a multi-target therapeutic strategy for T2DM. Most of the compounds are commercially unavailable and their properties have not yet been studied. Although most experiments are preclinical, the use of cell-based assays, HET-CAM models, and in vivo pilot studies (e.g., in diabetic mice) lays the groundwork for future pre-clinical trials. The author's contribution to the field is further evidenced by his extensive publication record in high-impact journals.

Reviewer's questions for the habilitation thesis defence (number of questions up to the reviewer)

1. The author has observed contradictory effects of some compounds (e.g., piceatannol, diplacone) in different tests. How is it possible that the same compound shows pro-oxidative activity in chemical tests and antioxidant activity in cell tests? Does it make sense to use chemical methods, and when?
2. The use of nanoparticles and encapsulation is considered a promising method for increasing bioavailability. The results of the study show that this does not always work. Does the author therefore recommend using this method for phenolic compounds, and under what conditions? How does the author explain that in some cases, a mixture of encapsulated and free substances (curcumin) was the most effective?
3. The author studied the activity of more than 10 structurally related compounds. What structural characteristics of these compounds are significant in terms of individual biological activities (structure-activity studies)?
4. Diplakon, diplacol, and moracin M appear promising for potential use in medicine. How difficult is it to obtain these compounds in large quantities? Is synthesis or semisynthetic production possible? What chemical modification would the author recommend to increase bioavailability and activity?
5. The work studies compounds, most of which are not commercially available. They were isolated directly from plants. How many compounds did the author study? Which is the rarest?
6. The work is very complex and includes methods of compound isolation, chemical, biological, and in vivo tests. Which steps the author specifically carried out?
7. The work has brought findings with potential applications in therapy. What are the main challenges in translating these findings into clinical applications?

Conclusion

The habilitation thesis entitled "Natural phenolics in alleviation of symptoms and complications of type 2 diabetes mellitus" by PharmDr. Jakub Tremel, Ph.D. **fulfils** requirements expected of a habilitation thesis in the field of "Molekulární biologie a genetika".

Date: 2.12. 2025

Signature: prof. MUDr. Iva Slaninová, Ph.D.

