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Magdalena Kubuj
Referent
Dział Obsługi Rady ds. Nauki i Doktorantów WUM
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**Review of the doctoral dissertation of
Maciej Korczak entitled:**

*Strategies of utilizing bioactive potential of natural products-derived
postbiotic metabolites*

It is a pleasure to serve as referee for Maciej Korczak's PhD thesis

"Strategies of utilizing bioactive potential of natural products-derived postbiotic metabolites".

Maciej Korczak's thesis is submitted as a cumulative work with three publications, of which Maciej Korczak is the first author:

Maciej Korczak, Maciej Pilecki, Sebastian Granica, Aleksandra Gorczyńska, Karolina Aleksandra Pawłowska, Jakub Patryk Piwowski. *Phytotherapy of mood disorders in the light of microbiota-gutbrain axis. Phytomedicine.* 2023 Mar;111:154642. doi: 10.1016/j.phymed.2023.154642. Review

Korczak M, Roszkowski P, Granica S, Piwowski JP. *Conjugates of urolithin A with NSAIDs, their stability, cytotoxicity, and anti-inflammatory potential. Scientific Reports.* 2022 Jul 8;12(1):11676. doi:10.1038/s41598-022-15870-8. Erratum in: *Scientific Reports.* 2022 Nov 2;12(1):18503.

Korczak M, Roszkowski P, Skowrońska W, Żołdak KM, Popowski D, Granica S, Piwowski JP. *Urolithin A conjugation with NSAIDs inhibits its glucuronidation and maintains improvement of Caco-2 monolayers' barrier function. Biomedicine & Pharmacotherapy.* 2023 Dec 31;169:115932. doi:10.1016/j.biopha.2023.115932.

Maciej Korczak is credited with 70-80% of the papers, which is a solid and strong basis for assessing his qualifications.

In addition to these three publications, Maciej Korczak signed three other papers as a co-author (*Eur J Pharmacol, Food Chem, Food Res Int*).

In his thesis, Maciej Korczak gives an extensive introduction to the topic of his work, covering about 16 pages, before discussing the above publications in more detail: he discusses the role of natural products as a still important source of bioactive compounds. He then introduces the reader to recent developments in microbiota and postbiotic metabolites. He gives definitions of prebiotics, probiotics, synbiotics and postbiotics and distinguishes the latter from the postbiotic metabolites that are the focus of the thesis. The introduction summarizes recent advances in the field.



Maciej Korczak lists three strategies as the aim of his thesis:

1. Focus on postbiotic metabolites of clinically effective herbal preparations used to treat mood disorders, such as depression and anxiety.
2. Derivatizing postbiotic metabolites to improve pharmacokinetic or pharmacodynamic properties.
3. To explore alternative routes of postbiotic metabolite administration (e.g. via the skin) to avoid phase I/II metabolism.

Aim 1 via literature search resulted in a review article in *Phytomedicine*. The author used the acquired new knowledge for project applications.

Aim 2 led to the synthesis of urolithin derivatives, i.e. their conjugation with NSAIDs such as ibuprofen, to increase the bioavailability by inhibiting the detoxification mainly in the intestinal wall. This strategy led to two publications in *Scientific Reports* and *Biomedicine & Pharmacotherapy*, respectively.

Aim 3 involved the synthesis of urolithin and a formulation for its topical application. This strategy did not result in a publication for funding and commercialization reasons.

The conclusions drawn from the work are listed on 2.5 pages, which may have profited from including also limitations of the data produced. This can be, however, discussed in the defence of the thesis.

In summary, the thesis covers an extremely broad area of research using chemical synthesis and analysis, cellular and *in vitro* assays, and cell and molecular biology techniques. The author has thus gained an unusually broad and extensive experience on both sides of pharmaceutical research, chemistry and biology.

The fact that a PhD student takes on such a challenge is very commendable. The fact that he is successful and productive with such a broad approach is an outstanding achievement.

One point of criticism from my side is the written form of the work. The language is sometimes flowery and complicated, and sometimes hard to understand. This also applies to the title of the thesis. My recommendation to the doctoral candidate would therefore be to practice clear and simple language, since science depends on being understood, - and I expect the candidate to remain in science.

Overall, there is no doubt that Maciej Korczak has made an enormous effort to collect the literature and data published in his thesis. The work is highly relevant.

I recommend that the thesis be accepted without any reservations.

Verena M. Dirsch