

Anti-obesity molecules of natural origin

Milen I. Georgiev^{*1,2}, Martina S. Savova^{1,2}, Saveta G. Mladenova³

¹Laboratory of Metabolomics, Institute of Microbiology, Bulgarian Academy of Sciences, 4000 Plovdiv, Bulgaria

²Center of Plant Systems Biology and Biotechnology, 4000 Plovdiv, Bulgaria

³BB-NCIPD Ltd., BB-National Centre of Infectious and Parasitic Diseases, Ministry of Health, 1000 Sofia, Bulgaria

Abstract

Obesity has outreached the dimensions of a health problem and has established as a global epidemic (named Globesity) over the past decades (Jaaks et al., 2019; NCD-RisC, 2019). Excessive body weight appears among the top five risk factors in terms of attributable deaths and metabolic complications development (NCD-RisC, 2019; Stefan, 2020). Consequently, management of obesity (i.e., prevention and treatment) is subject of undergoing intense research (Flaherty et al., 2019).

Natural compounds attracted profound interest as candidates for obesity management. We have examined the potential of plant extracts and their bioactive principles to affect adipogenic differentiation in human adipocytes (Savova et al., 2021; Mladenova et al., 2022). Their mechanism of action was studied in-depth by using transcriptional analysis through real-time quantitative PCR and protein abundance evaluation by Western blotting. The key adipogenic transcription factors – peroxisome proliferator-activated receptor gamma (PPAR γ) and CCAAT-enhancer-binding protein alpha (C/EBP α) – appeared strongly decreased at a protein level by treatments with plant extracts and pure compounds. Moreover, the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway was found to be involved in the anti-adipogenic effect of the plant extracts and pure molecules. Collectively, our findings indicate that selected plant extracts (and their active principles) hampered adipocyte differentiation through PI3K/AKT inhibition. Among selected compounds, betulinic acid and maackiain exhibit the most promising anti-adipogenic activity (Savova et al., 2021; Mladenova et al., 2022). Furthermore, the research has been translated from human

adipocytes to the organism model of *Caenorhabditis elegans*.

Acknowledgments

This research received funding from the European Union's Horizon 2020 research and innovation programme, project PlantaSYST (SGA No 739582 under FPA No. 664620).

References

- Flaherty, S.E., Grijalva, A., Xu, X., Ables, E., Nomani, A., Ferrante, A.W.Jr., 2019. A lipase-independent pathway of lipid release and immune modulation by adipocytes. *Science*. 363(6430), 989-993.
<https://doi.org/10.1126/science.aaw2586>.
- Jaacks, L.M., Vandevijvere, S., Pan, A., McGowan, C.J., Wallace, C., Imamura, F., Mozaffarian, D., Swinburn, B., Ezzati, M., 2019. The obesity transition: stages of the global epidemic. *Lancet Diabetes Endocrinol.* 7(3), 231-240.
[https://doi.org/10.1016/S2213-8587\(19\)30026-9](https://doi.org/10.1016/S2213-8587(19)30026-9)
- Mladenova, S.G., Savova, M.S., Marchev, A.S., Ferrante, C., Orlando, G., Wabitsch, M., Georgiev, M.I., 2022. Anti-adipogenic activity of maackiain and ononin is mediated via inhibition of PPAR γ in human adipocytes. *Biomed. Pharmacother.* 149-112908.
<https://doi.org/10.1016/j.biopha.2022.112908>
- NCD Risk Factor Collaboration (NCD-RisC), 2019. Rising rural body-mass index is the main driver of the global obesity epidemic in adults. *Nature* 569, 260-264.
<https://doi.org/10.1038/s41586-019-1171-x>
- Savova, M.S., Vasileva, L.V., Mladenova, S.G., Amirova, K.M., Ferrante, C., Orlando, G., Wabitsch, M., Georgiev, M.I., 2021. *Ziziphus jujuba* Mill. leaf extract restrains adipogenesis by targeting PI3K/AKT signaling pathway.

Biomed. Pharmacother. 141:111934.

<https://doi.org/10.1016/j.biopha.2021.111934>

Stefan, N., 2020. Causes, consequences, and treatment of metabolically unhealthy fat distribution. *Lancet Diabetes Endocrinol.* 8, 616-627.