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IN SILICO STUDIES OF PLANT TRITERPENOIDS: PHARMACOPHORE-BASED VIRTUAL SCREENING AND TOXICITY EVALUATION

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Statement of the Problem: The metabolic syndrome (MS) represents a complex pathological condition featured by hypertension, type 2 diabetes (T2D) and obesity. It is among the risk factors for development of cardiovascular diseases (CVD) and is characterized by increasing global prevalence. Modulation of the nuclear peroxisome proliferator-activated receptor γ (PPARγ) by natural compounds is considered a promising pharmacological strategy for targeting the MS. Within this study, we aimed at applying a virtual screening protocol for investigating the potential of triterpenoid sapogenins of natural origin to act as PPARγ partial agonists. Furthermore, an in silico estimation of their safety profile has been performed.

Methodology & Theoretical Orientation: An in-house virtual library with more than 70 triterpenoids had been screened by a pharmacophore-based docking of the unique aglycons in the PPARγ binding pocket using MOE software (v.2016.0802). The toxicity of these aglycons was evaluated using Derek Nexus knowledge-based system (v.5.0.1.).

Findings: Potential partial agonist-like binding modes were evaluated based on the binding energy scores of the protein-ligand (PL) complexes resulting from the docking simulation. The PL interactions and poses relevant to the PPARγ partial agonists' binding pattern were predicted. Potential toxicity effects, including chromosome damage and developmental toxicity, were outlined for particular triterpenoid aglycons.

Conclusion & Significance: The results of this study contribute to the mechanistic explanation at molecular level of the effects of triterpenoid saponins/sapogenins by a potential PPARγ-mediated mode of action. This research can direct further studies of naturally-derived triterpenoids as potential MS modulators.

Recent Publications

1. Al Sharif M, Alov P, Diukendjieva A, Vitcheva V, Simeonova R, et al. (2017) Molecular determinants of PPARγ partial agonism and related *in silico/in vivo* studies of natural saponins as potential type 2 diabetes modulators. Food Chem Toxicol 112:47–59.
2. Al Sharif M, Alov P, Vitcheva V, Diukendjieva A, Mori M, et al. (2017) Natural modulators of nonalcoholic fatty liver disease: Mode of action analysis and in silico ADME-Tox prediction. Toxicol Appl Pharmacol 337:45–66.
3. Al Sharif M, Tsakovska I, Pajeva I, Alov P, Fioravanzo E, et al. (2017) The application of molecular modelling in the safety assessment of chemicals: A case study on ligand-dependent PPARγ dysregulation. Toxicology 392:140–154.
4. Tsakovska I, Al Sharif M, Alov P, Diukendjieva A, Fioravanzo E, et al. (2014) Molecular modelling study of the PPARγ receptor in relation to the mode of action/adverse outcome pathway framework for liver steatosis. Int J Mol Sci 15:7651–66.
5. Al Sharif M, Alov P, Vitcheva V, Pajeva I and Tsakovska I (2014) Modes-of-action related to repeated dose toxicity: tissue-specific biological roles of PPAR γ ligand-dependent dysregulation in nonalcoholic fatty liver disease. PPAR Res. 2014:432647.

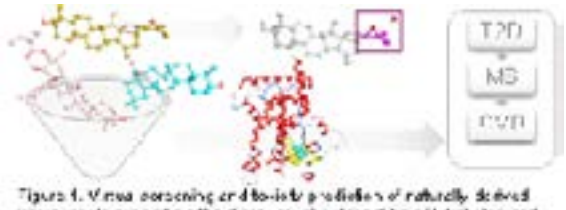

Figure 1. Virtual screening and in-silico predictions of naturally derived triterpenoids supporting the discovery of potential type 2 diabetes and metabolic syndrome modulators and the prevention of cardiovascular diseases development.

Biography

Merilin Al Sharif got her BS Degree in Biotechnology and MS degree in Biochemistry from Sofia University "St. Kliment Ohridski", Faculty of Biology, and PhD in Biological Sciences from the Bulgarian Academy of Sciences (BAS). Currently she holds the position of a Senior Assistant Professor at the Institute of Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences. Her main scientific interests relate to predictive toxicology and in silico drug design. Her most recent investigations in the field of naturally-derived triterpenoids could aid in the discovery of promising leads for design of PPARγ-targeting modulators of the metabolic syndrome.

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