University of Naples Federico II

Department of Pharmacy

International PhD course in

Nutraceuticals, Functional Foods and Human Health

AI-Assisted Identification and Design of Nutraceutical Modulators of Nuclear Receptors for the Treatment of Metabolic Diseases

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Nuclear receptors (NRs) are a class of ligand-dependent transcription factors that regulate gene expression in response to metabolic and environmental signals. These receptors, including PPARs (α, β/δ, γ), FXR, RXR, and LXR, play a central role in controlling lipid and glucose homeostasis, insulin sensitivity, and energy balance.[1] Selective modulation of NRs is emerging as a promising therapeutic approach for metabolic diseases such as type 2 diabetes, NAFLD/NASH, and metabolic syndrome.[2] However, identifying effective and safe ligands with high selectivity and low toxicity remains a significant challenge.[3,4] In this context, natural products (NPs) and nutraceuticals represent a valuable and largely underutilized source of bioactive molecules with potential for NR modulation. Their high structural diversity and long history of use in traditional medicine make them ideal candidates for exploring new modulators. Well-known examples like amorfrutins and other polyphenols active on PPARs demonstrate that NPs can act as partial agonists, dual agonists, or antagonists with favorable pharmacological profiles.[5-8] The objective of this project is to identify new NR modulators through an integrated computational approach. This approach will combine deep learning methodologies,[9] docking, molecular dynamics, and prediction of biological activity (QSAR) and ADMET properties,[10] leveraging information available in natural product libraries derived from functional foods, medicinal plants, and marine sources.[11-13] Project activities will be conducted at the Laboratory of Excellence in Molecular Modeling (LMM). The most promising compounds will undergo *in vitro* biological testing, including transactivation assays, target gene expression analysis, and metabolic analyses to evaluate their effects on lipid and glucose metabolism. The project aims to contribute to the discovery of new nutraceuticals, promoting a precision medicine approach for the prevention and treatment of metabolic diseases.

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