University of Naples Federico II

Department of Pharmacy

International PhD course in

Nutraceuticals, Functional Foods and Human Health

Computational investigation of bioactive natural compounds and environmental toxins: from molecular mechanisms to therapeutic targets

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Project description

Natural compounds and their structural analogues have long been a primary source of bioactive molecules. However, in many cases, the structural/conformational features responsible for their activity or toxicity remain poorly understood, and identifying their molecular targets can be challenging. On the other hand, toxins of various origins can contaminate food and the environment, potentially causing a range of health issues in humans.

In this context, the present project aims to investigate the structure–activity relationships of bioactive natural compounds and contaminants found in food and/or the environment in order to: i) define their molecular mechanisms of action; ii) predict the activity/toxicity of structural analogues; iii) guide structural modifications to explore their potential as lead compounds for the protection of human health. The research will be conducted using an integrated computational approach based on various techniques (i.e., molecular dynamics and mechanics calculations, DFT calculations, structural and bioinformatics analysis, 3D database mining, and docking studies). The results obtained will be combined with experimental studies.

In particular, based on current collaborations[3-8], the research will be carried out within multidisciplinary projects, and the following molecular targets will be considered: the proteasome, viral proteins (e.g., coronavirus), enzymes targeted by antiparasitic drugs, and calcium channels. On the other hand, the main contaminants to be studied will include marine toxins such as palytoxin, as well as protein toxins such as prions. Prions represent a unique class of infectious protein agents responsible for severe neurodegenerative encephalopathies[9,10]. Their pathological form, known as PrP^{Sc} (scrapie), is characterized by an abnormal folding of the cellular prion protein (PrP^{C}), which acquires infectious and aggregating properties. Recent studies have highlighted their ability to persist in the environment, particularly in soil, where they can remain infectious for years[11]. As part of this project, we aim to study the molecular mechanisms underlying the conversion of PrP^{C} to PrP^{Sc}, with the goal of identifying physicochemical factors that promote this transition. In parallel, therapeutic and/or diagnostic compounds will be designed and tested for the early detection of the pathological form. The approach will integrate computational screening, chemical synthesis, and biological validation, addressing prions both as persistent environmental contaminants and as therapeutic targets.

The computational studies will be carried out using all the software and computing resources available at the Laboratory of Excellence in Molecular Modeling (https://www.farmacia.unina.it/laboratori-di-eccellenza/lmm).

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FUNDS

1)PRIN – Bando 2022 PNRR: Prot. P2022YRPHS; Title: Multifaced-peptidomimetics as proteasome modulators.

2)PRIN – Bando 2022: Prot. 2022MBK24T; Title: UNmasking VIral RNA: targeting viral RNA capping machinery to tackle COVID-19 and future CoV emergencies (UNVIR-19)

3)PRIN – Bando 2022: Prot. 2022PAAYZE; Title: Modulating confoRmational Equilibria of prion protein and proteaSome to tune protEostasis neTwork (RESET).

4)COST Action CA21111. One Health drugs against parasitic vector borne diseases in Europe and beyond (OneHealthdrugs).